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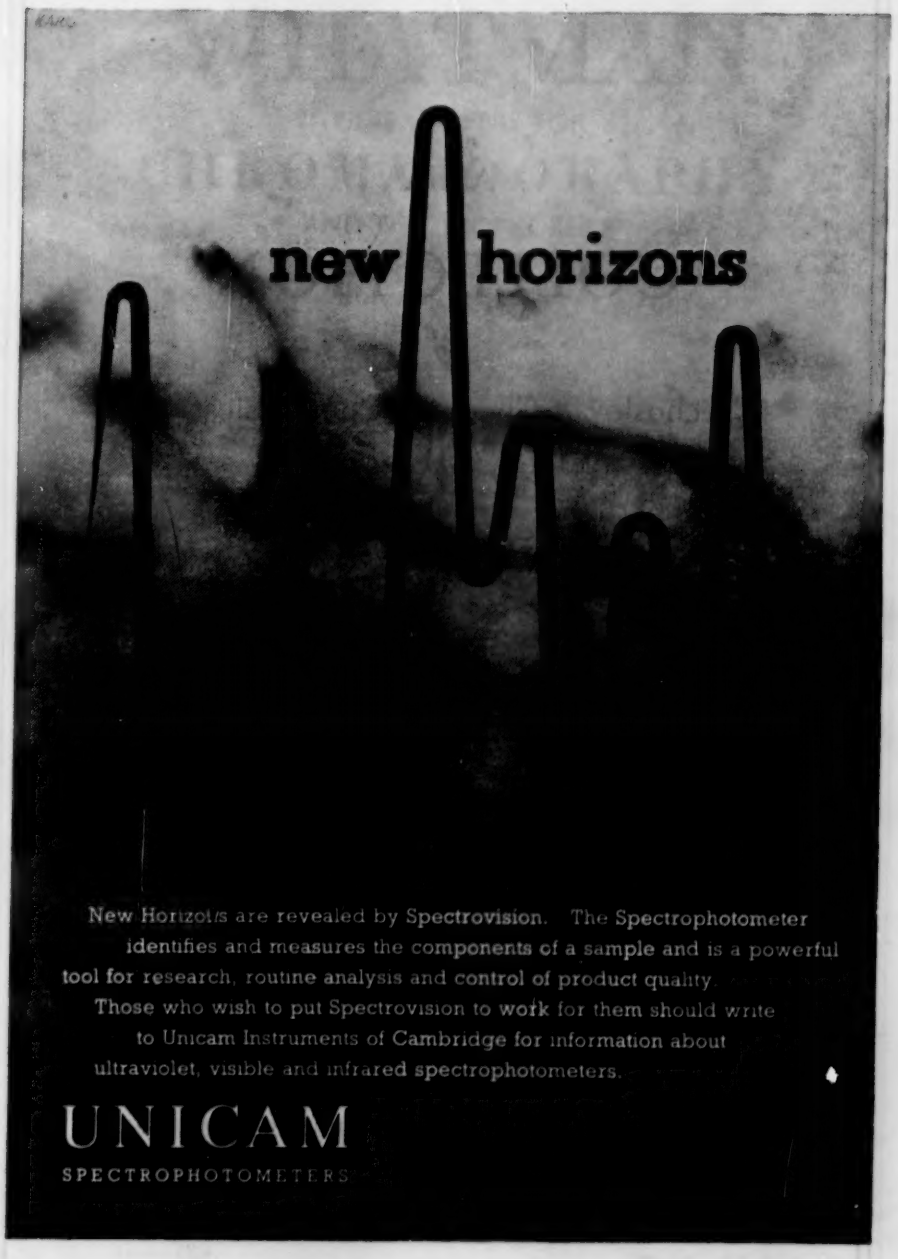
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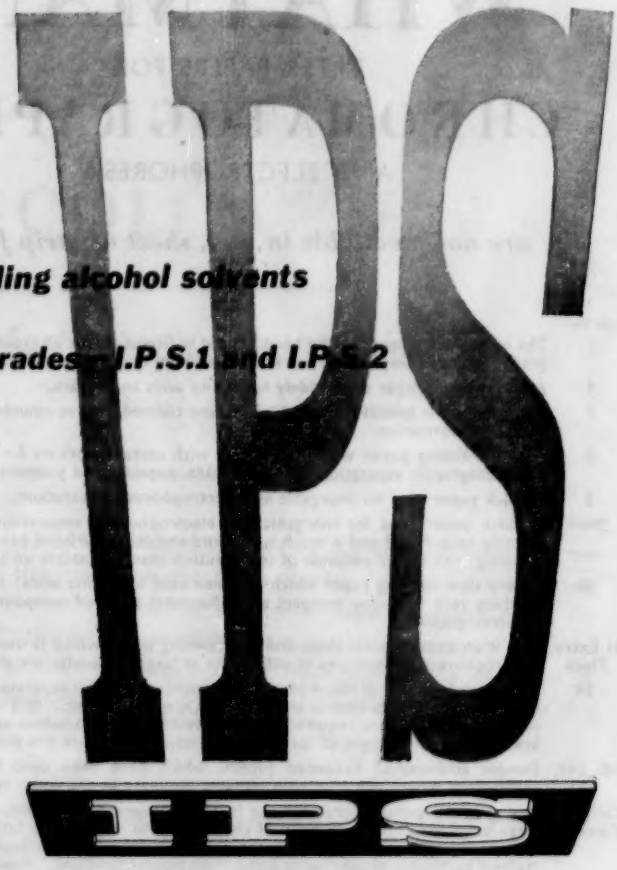

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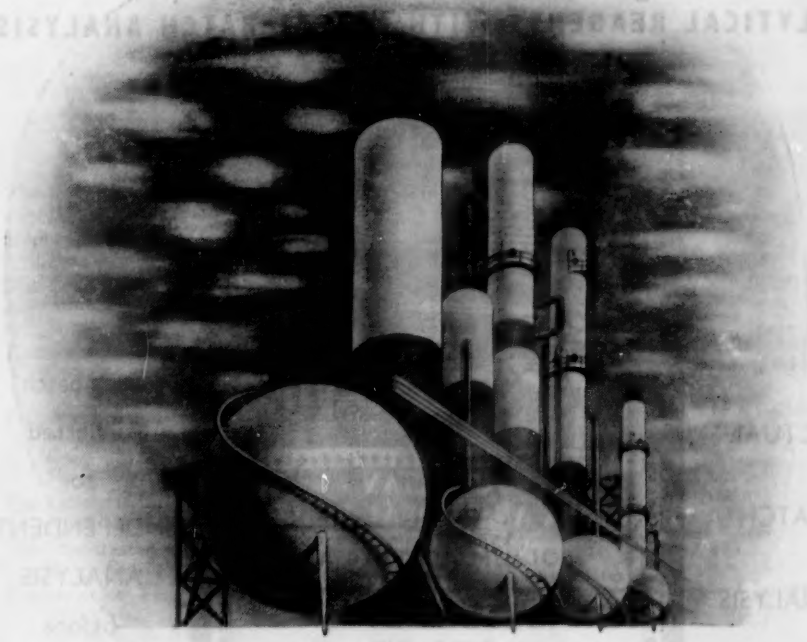

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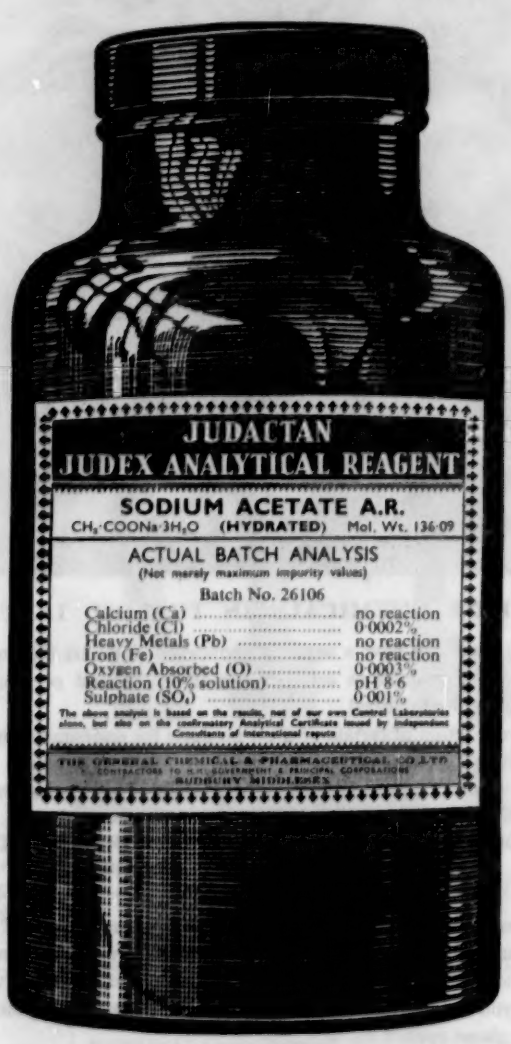
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Attention is also drawn to changes in the method of quoting references (cf. *Proceedings*, July).

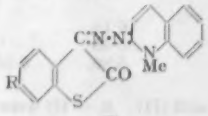
mero*Cyanines Derived from Thio-oxindole. Part IV.* The Isomerism of the Diazadimethin*mero*cyanines.*

By R. H. Glauert and Frederick G. Mann.

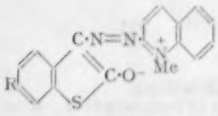
[Reprint Order No. 6203.]

It is shown that the isomerisation of these diazadimethin*mero*cyanines, briefly recorded in Part II, is a common property of the four members of the series which have been prepared, but it has not been detected in the analogous dimethin*mero*cyanines. The conditions of the isomerisation and the probable nature of the isomerism are discussed.

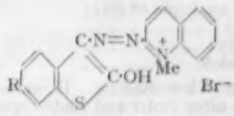
We have previously recorded (*J.*, 1952, 5012) that the reddish-brown [3-(2 : 3-dihydro-2-oxothionaphthen)][2-(1 : 2-dihydro-1-methylquinoline)]diazadimethin*mero*cyanine (I; R = H), when treated in warm acetone solution with hydrobromic acid, forms an orange-yellow hydrobromide, which, in view of its marked colour, was considered to be a true cyanine of structure (II). Analogous dimethin*mero*cyanines show a similar salt formation (Glauert and Mann, *J.*, 1952, 2135). The orange [3-(2 : 3-dihydro-2-oxothionaphthen)][2-(3-ethylbenzothiazoline)]diazadimethin*mero*cyanine (III; R = H), m. p. 175—176°, however, when either treated in cold acetone with hydrobromic acid or boiled in acetic acid, was converted into a bright orange isomer, m. p. 259—260°. We have now investigated these reactions more fully, and find that both salt formation and isomerisation occur in all the four diazadimethin*mero*cyanines of type (I) and (III) at present available.



(I)



(*IA*)



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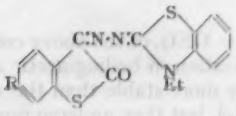
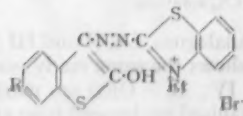


(III)



(IV)

The *mero*cyanine (I; R = H), m. p. 225—226°, was unaffected when its ethanolic solution was boiled for 24 hours, but its solution in acetic acid, when boiled for 3 hours, gave an orange isomer, m. p. 236—237° : a mixture of the two forms melted slowly between 213° and 235°. A solution of each form in boiling hydrobromic acid gave the hydrobromide (II; R = H), m. p. 212°; this salt was sufficiently stable to allow recrystallisation from acetic acid, but addition of water to its cold ethanolic solution caused dissociation and deposition of the low-melting form of (I; R = H). The ultraviolet and visible spectra of the two forms in ethanol were almost identical, the low- and the high-melting form showing a main band at $\lambda_{max.}$ 470—472 mμ (ε 35,800) and 472 mμ (ε 37,500) respectively. On the other hand, the infrared spectra of the crystalline isomers were in general quite different (for example, that of the low-melting form showed a strong band at 9·98 μ which was absent in that of the isomer), but the two forms showed the CO band at 5·99 and 5·95 μ respectively (see Table).

We have investigated in greater detail the isomerism of the thiazoline *mero*cyanine (III; R = H), for the considerable difference in the m. p.s of the isomers facilitates their study : moreover the interconversion of the isomers apparently occurs more readily than in the quinoline series. In view of the fact that hydrobromic acid, when added to a cold acetone solution of the low-melting compound, causes such ready isomerisation, it is particularly noteworthy that both isomers when dissolved in hot hydrobromic acid give an unstable orange-yellow hydrobromide, presumably (IV; R = H), which on attempted recrystallisation from

* Parts II and III, *J.*, 1952, 5012; 1955, 28.

ethanol regenerates the low-melting form, but on slow heating gives the high-melting form. Although acids promote the isomerisation, they are not essential : a sample of the low-melting form, when kept at 200° for 15 min., underwent solidification with conversion into the high-melting form, m. p. 260°. Similarly a mixture of the two isomers when rapidly heated melted at 230—250°, but when slowly heated melted at 260°. Solutions of the low-melting form in benzene and in ethanol, when boiled for a short time and then set aside in closed flasks, deposited the high-melting form in 12 hours and 3—4 days respectively : chance inoculation of these solutions with the high-melting isomer was improbable. The latter isomer was unaffected when its solution in ethanol–triethylamine was boiled for 1 hour, so that bases do not apparently reverse the isomerisation. The two isomers resembled those of (I; R = H) in that their ultraviolet and visible absorption spectra were almost identical, whereas their infrared spectra were markedly different, except that they showed the CO band at 5·90 and 5·89 μ respectively : these values moreover were virtually unchanged in carbon disulphide solution (see Table).

	Visible spectra. Main band, in mμ, followed by ε values ( )		Infrared spectra. Bands in CO region and in 10-μ region [ ]	
	L.-m. isomer	H.-m. isomer	L.-m. isomer	H.-m. isomer
(I; R = H)	470—472 (35,800)	472 (37,500)	5·99 [9·98]	5·95
(I; R = OEt)	—	—	5·90 [9·97]	5·90
(III; R = H)	454—455 (26,400)	454—458 (25,300)	5·90 [10·00]	5·89
,,	—	—	5·87 * [10·07] *	5·85 *
(III; R = OEt)	—	—	5·89 [10·08]	5·87
Dimethin analogue of (I; R = H)	553		6·15	[9·91]
Dimethin analogue of (III; R = H)	531		6·10	
Thioindoxyl	—		5·85	
Thio-oxindole	—		5·80,	5·76 *

L.-m. = low-melting. H.-m. = high-melting.

The ultra-violet and visible spectra of compounds (I; R = H) and (III; R = H) were measured in ethanol, and those of their dimethin analogues in methanol.

* Measured in CS_2 solution.

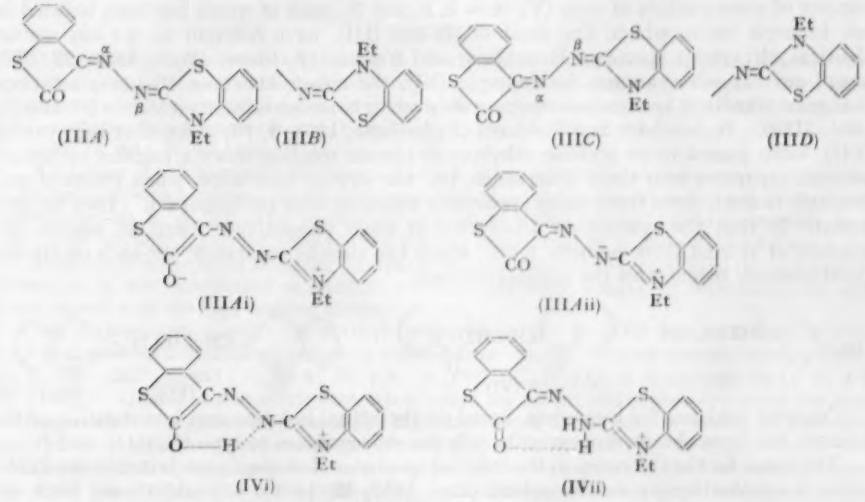
The 6-ethoxy-analogues, *i.e.*, (I and III; R = OEt), of the above compounds have been prepared. Each shows the same ready isomerisation in boiling acetic acid. Their hydrobromides (II and IV; R = OEt) are markedly more stable than the unsubstituted salts, and can be recrystallised unchanged from ethanol, but they undergo rapid hydrolysis in hot aqueous ethanol or ethanolic pyridine, liberating the low-melting isomer. The infrared spectra of each pair of isomers show the same relationship as those of (I and III; R = H).

It is noteworthy that the infrared spectra of all four low-melting isomers show a strong band at *ca.* 10 μ (see Table), which is absent in those of the high-melting isomers. The significance of this band is uncertain, but it has been selected to exemplify the considerable difference between the spectra of each pair of isomers.

The above evidence leaves no doubt that each pair of the above four compounds represents true isomers, and that no question of dimorphism is involved. It is significant, moreover, that the dimethin analogues of (I and III; R = H), which are unaffected by boiling acetic acid and have given no evidence of isomerisation, show a carbonyl band at 6·15 and 6·10 μ respectively, whereas this band in the above four pairs of diazadimethin compounds falls between 5·87 and 5·99 μ. This indicates strongly that in the diazadimethin compounds the contribution of polar forms such as (I*A*) is much smaller than in the dimethin analogues. This deduction is supported (*a*) by the more intense colour of these analogues and (*b*) by the fact that thioindoxyl and thio-oxindole, which cannot show this marked charge separation, have their CO bands at 5·85 and 5·80 μ respectively (see Table).

The above data are insufficient to provide a decisive explanation of the isomerism of these diazadimethin compounds, and of the apparent absence of isomerism in their dimethin analogues. We would however tentatively put forward an explanation based on the following considerations. The diazadimethin compounds, for example (III), can theoretically

exist (in their covalent state) in four geometrically isomeric forms, namely, (III*A* and *B*), in both of which the β-nitrogen atom is the *cis*-position to the CO group, but the NEt group is in the *cis*-position to this atom in (III*A*) and in the *trans*-position in (III*B*); and (III*C*) and (III*D*), in both of which the β-nitrogen is *trans* to the CO group, but which are otherwise analogous to (III*A*) and (III*B*): four other conformations are precluded because they would entail overlapping of the two heterocyclic nuclei. The dimethin analogues could also show forms similar to (III*A*, *B*, *C*, and *D*). Each of the diazadimethin forms differs from its dimethin analogue, however, in that it has an extra polar form: for example, (III*A*) would receive contributions from the polar forms (III*A*i) and (III*A*ii). The contribution of (III*A*ii) must weaken that of (III*A*i), and may well be the reason why the infrared spectra show that the CO group is uniformly less strongly polar in the diazadimethin compounds than in the dimethin analogues. Furthermore, salt formation with (III*A*i) and (III*A*ii) would give the cations (IVi) and (IVii) respectively, which are in practice indistinguishable: in this cation, which would be markedly stabilised by the hydrogen-bonding, the benzothiazole group may have some rotational mobility about the βN–C link and will therefore adopt the most stable position, in which case the isomer (III*B*) would give the same cation. The *trans* isomers (III*C*) and (III*D*) could not form a cation of this type without intermediate conversion into the *cis*-analogues.



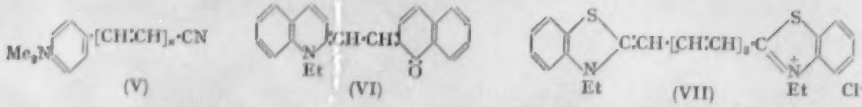
We suggest therefore that in all four diazadimethin compounds investigated, the low-melting isomer may have the *cis*-structure, being of type (III*A*) or (III*B*), and that the high-melting isomer has the *trans*-structure of type (III*C*) or (III*D*). The greater stability of the high-melting isomer, shown by the conversion low-melting ⟶ high-melting form, which may occur (with speed dependent on the particular compound) slowly in cold solvents, more rapidly in boiling solvents, and very readily on heating, is possibly due to the opposition of the dipoles on the negatively-charged oxygen and nitrogen atoms in (III*A*i) and (III*A*ii) respectively, which would become much weaker in the corresponding *trans*-forms. This interconversion is clearly not a difficult process; consequently a hot strong acid such as boiling 48% hydrobromic acid would convert each isomer into the most stable cation, *i.e.*, that of the *cis*-form (IVi ⟷ ii). This salt, on dissociation under mild conditions, would retain its essential conformation and hence hydrolysis gives the low-melting isomer throughout. It is probable moreover that in the preparation of the diazadimethin compounds of type (I) and (III) (cf. Part I), the initial reaction is the condensation of the thio-oxindole 3-hydrazone with 2-iodoquinoline methiodide and with 2-ethylthiobenzothiazole ethiodide,

with liberation of hydrogen iodide and ethanethiol respectively, and with the formation in each case of the iodide of the cation (IV i ⟷ ii) : the main function of the triethylamine is then to hydrolyse this salt, and thus the low-melting *cis*-isomer arises in all these preparations.

A very low hydrogen-ion concentration would appear to accelerate the normal *cis* → *trans* conversion, being unable to arrest this process at the intermediate cation stage : hence the low-melting isomer always in boiling acetic acid, and in the one case of (III ; R = H) in warm acetone containing hydrobromic acid, is converted into the high-melting isomer.

The above considerations regarding the structural significance of salt formation will not apply to the dimethin analogues, in which however the >C:CH·CH:C< chain must for similar steric reasons also have the *trans*-form. The unlike terminal heterocyclic rings could again theoretically arrange themselves in *cis*- and *trans*-positions relative to one another. The fact that isomerism was never encountered in the numerous examples of these compounds studied (Glauert and Mann, *loc. cit.*) may indicate that these rings always adopt the most stable relative positions, and that similarly in the diazadimethin series only one member of each pair, (III*A*) or (III*B*), and (III*C*) or (III*D*), is actually formed.

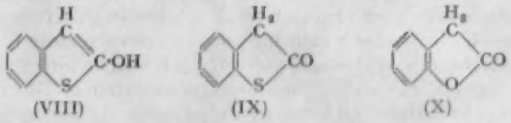
There is evidence for similar isomerism in other types of *mero*cyanines, and possibly in true cyanines. Coenen and Pestemer (*Z. Elektrochem.*, 1953, **57**, 785) have described a number of *mero*cyanines of type (V ; n = 1, 2, and 3), each of which has been isolated in two isomeric forms, which, like those of (I) and (III), have different m. p.s but almost identical ultraviolet spectra. Hirschberg and Fischer (*J. Chem. Phys.*, 1954, **22**, 572) record several *mero*cyanines, for example (VI), the colour of whose ethanolic solutions changes markedly at low temperature, possibly owing to isomeric interconversion (cf. also *J.*, 1954, 3129). Zechmeister and Pinckard (*Experientia*, 1953, **9**, 16) claim that the cyanine (VII), when passed in an acetone–ethylene dichloride solution down a calcium carbonate column, separates into three blue zones, but the dye in each zone, when removed and similarly treated, gives three zones apparently identical with the initial set. They suggest tentatively that the cyanine on dissolution at room temperature forms an equilibrium mixture of at least three isomeric forms, which can thus be separated, but each on elution spontaneously regenerates the original mixture.



(V) (VI) (VII)

Concrete evidence for isomerism, based on the actual isolation and investigation of the isomers, has been obtained apparently only for *mero*cyanines of type (I), (III), and (V).

The value for the CO group in the infrared spectrum of thio-oxindole, cited in the Table, raises a noteworthy point. Marschalk (*Ber.*, 1912, **45**, 1481 ; *J. prakt. Chem.*, 1913, **88**, 227) isolated thio-oxindole in two forms, m. p. 33—34° and 44—45°, which were very readily interconvertible : for example, steam-distillation gave the high-melting form, which when dried and distilled at atmospheric pressure gave the low-melting form. Komppa and Weckmann (*J. prakt. Chem.*, 1933, **138**, 109) decided that the low- and the high-melting product were probably the enol and the keto-form, (VIII) and (IX), respectively. Störmer (*Annalen*, 1900, **313**, 83) isolated *iso*coumaranone (X) in two forms, m. p. 28—28·5° and 49°, which were also very easily interconvertible.



(VIII) (IX) (X)

We have obtained thio-oxindole in two forms, m. p. 33—33·5° and 44—45°, and also 6-ethoxy(thio-oxindole) in two forms, m. p. 38—40° and 47—48° (*J.*, 1952, 2217). We find that a crude sample of the low-melting form of thio-oxindole, when confined in a desiccator

at atmospheric pressure, changes to the high-melting form in *ca.* 7 days, but a pure sample remains unchanged for at least a month. The low-melting form can be recrystallised unchanged from aqueous ethanol, and its solutions in methanol and acetonitrile, when allowed to evaporate spontaneously, deposit the unchanged material, whereas those in carbon disulphide, chloroform, and carbon tetrachloride deposit the high-melting form. Each form, when dissolved in ice-cold aqueous potassium hydroxide which is then carefully acidified, is deposited unchanged. The infrared spectrum of the high-melting form in a Nujol mull, or as a solid film, showed CO absorption at 5·80 μ, with no indication of the presence of an OH group or of a double bond : the value for the CO absorption was virtually unchanged in carbon disulphide solution (see Table), so intermolecular hydrogen-bonding is absent. The spectrum of the low-melting form in the mull was unreliable owing to the possible onset of conversion, but in methanol solution it showed strong CO absorption at 5·78 μ, with absence of a double bond. Although in the enol form (VIII) the double bond in the " aromatic " thiophen ring would probably not give the normal ethylene band, the CO absorption in both forms gives a strong indication that they are dimorphic forms and not isomeric compounds. The earlier chemical evidence for isomerism must be treated with reserve, because their ready transformation might be strongly influenced by the nature of the reagent applied. The values for thio-oxindole quoted in the Table are those obtained with the high-melting form.

Experimental

[3-(2 : 3-*Dihydro*-2-*oxothionaphthen*)][2-(1 : 2-*dihydro*-1-*methylquinoline*)]*diazadimethin*mero*cyanine* (I; R = H).—A solution of this compound, m. p. 225—226°, in acetic acid, when boiled under reflux for 3 hr. and cooled, deposited the *isomer*, orange prisms, m. p. 236—237°, unchanged by recrystallisation from acetic acid (Found : C, 68·25; H, 4·6; N, 13·0. $C_{18}H_{12}ON_2S$ requires C, 67·7; H, 4·1; N, 13·14%).

A solution of this isomer in hot aqueous 48% hydrogen bromide gave, on cooling, an orange hydrobromide which, when collected and recrystallised (whilst damp) from ethanol, gave orange-brown crystals, m. p. 211—212° (decomp.) : a mixture of this salt and the hydrobromide, m. p. 210—211° (decomp.), derived from the low-melting isomer had m. p. 210—211° (decomp.).

Addition of water to an ethanolic solution of this hydrobromide precipitated the low-melting isomer, m. p. 225°, unchanged on admixture with an authentic sample but depressed to *ca.* 210° when mixed with the high-melting isomer.

The 6-*ethoxy*-analogue (I; R = OEt), prepared as (I; R = H) but with 6-ethoxythionaphthenquinone 3-hydrazone and recrystallised from ethanol, formed crimson needles (32%), m. p. 222—223° (Found : C, 65·6; H, 4·9; N, 12·0. $C_{20}H_{17}O_2N_3S$ requires C, 66·1; H, 4·7; N, 11·6%). Its solution in acetic acid, when boiled for 1·5 hr. and cooled, deposited the high-melting *isomer*, orange-red crystals, m. p. 233—234°, from acetic acid, depressed to 205—210° on admixture with the above compound (Found : C, 66·5; H, 5·05; N, 11·6%).

The addition of 48% hydrobromic acid to an acetone suspension of the low-melting isomer increased the temperature to *ca.* 40°, giving a clear orange-yellow solution which on cooling deposited the *hydrobromide trihydrate*, orange crystals, m. p. 209—210° inserted at 200° (Found : C, 48·6; H, 4·4; N, 8·7. $C_{20}H_{17}O_2N_3S,HBr,3H_2O$ requires C, 48·2; H, 4·85; N, 8·4%).

This hydrobromide recrystallised from ethanol as orange crystals of unchanged m. p. The addition of water to the ethanol solution precipitated the orange-red low-melting isomer (I; R = OEt) contaminated with the hydrobromide, the product after crystallisation from ethanol having m. p. 212—216° (preliminary softening), whereas the addition of a small quantity of pyridine to the original solution precipitated the pure red isomer, m. p. and mixed m. p. 220° after crystallisation from ethanol.

[3-(2 : 3-*Dihydro*-2-*oxothionaphthen*)][2-(3-*ethylbenzothiazoline*)]*diazadimethin*mero*cyanine* (III; R = H).—The conditions for the isomerisation of this compound have been described (Glauert and Mann, *loc. cit.*) : that caused by the addition of cold hydrobromic acid to an acetone solution of the low-melting form was erroneously stated to have been performed in acetic acid solution. The low-melting form, when kept at 200° for 10 min., remained as a clear liquid which when seeded with the high-melting form slowly solidified : when kept at 200° for 15 min., it spontaneously solidified. The product in each experiment, after crystallisation from ethanol, had m. p. 260° (alone and mixed). Each isomer gave, in boiling 48% aqueous hydrobromic acid, a yellow solution which on cooling deposited orange-yellow crystals of the *hydrobromide* (IV;

R = H), which, even when dried over calcium chloride in a vacuum, became red on the surface owing to slight dissociation (Found: C, 47·9; H, 4·3. $C_{17}H_{13}ON_3S_3$,HBr requires C, 48·6; H, 3·4%). Attempted recrystallisation of this salt from ethanol gave the low-melting isomer, m. p. and mixed m. p. 173—175°. The hydrobromide, when heated from room temperature or from 160°, had m. p. 249—251° with some previous shrinkage: when immersed and kept at 220° or 235° it shrank without melting. A mixture of this salt and the high-melting isomer (m. p. 259—260°), when immersed at 160° or 225°, had m. p. *ca.* 250°. It is clear therefore that this isomer is the ultimate product of thermal dissociation of the salt. A solution of the isomer, m. p. 259—260°, in ethanol–triethylamine (5 : 1 vol.) was boiled under reflux for 1 hr., and on cooling deposited the unchanged solute.

The 6-*ethoxy*-analogue (III; R = OEt), prepared as (III; R = H) but with 6-ethoxythionaphthenquinone 3-hydrazone, and recrystallised from ethanol formed the *hemiethanolate* (50%), orange-red needles, m. p. 197—198° (Found: C, 59·1; H, 4·7; N, 10·3. $C_{19}H_{17}O_2N_3S_2,0{\cdot}5C_2H_6O$ requires C, 59·1; H, 5·0; N, 10·3%). Its solution in acetic acid, when boiled for 3 hr. and cooled, deposited the high-melting *isomer*, orange prisms, m. p. 207—208° (after recrystallisation from acetic acid), depressed to 173—177° by admixture with the above compound (Found: C, 59·2; H, 4·7; N, 11·0. $C_{19}H_{17}O_2N_3S_2$ requires C, 59·5; H, 4·5; N, 11·0%).

The addition of 48% hydrobromic acid (5 c.c.) to a solution of the low-melting isomer (0·1 g.) in hot acetone (10 c.c.), followed by cooling and stirring, deposited the *hydrobromide* (IV; R = OEt), orange crystals from acetic acid (Found: C, 48·3; H, 4·7; N, 8·1. $C_{19}H_{17}O_2N_3S_2$,HBr,$C_2H_4O_2$ requires C, 48·1; H, 4·2; N, 8·0%). This salt had m. p. 201—203° (softening from 198°) when heated from room temperature or from 150°: inserted at 180°, it melted with decomp. Mixtures of the salt with the low- and the high-melting isomer, heated from 150°, had m. p. 198—202° and 204—206° respectively. Attempted ethanolic recrystallisation of the hydrobromide gave the low-melting isomer, sparkling red crystals, m. p. and mixed m. p., 197—198°. It is noteworthy that the hydrobromide (II; R = H) also separated with acetic acid (1 mol.) of crystallisation.

Attempted Isomerisation of Dimethin Analogues.—An acetic acid solution of the analogue, m. p. 254°, of the compound (I; R = H) was boiled under reflux for 3 hr. and cooled. The deposited material, when recrystallised from ethanol, afforded the unchanged compound, m. p. 252—253°, mixed m. p. 253—254°. The analogue, m. p. 226°, of the compound (III; R = H), when similarly treated, was recovered unchanged, having m. p. 228—229°, mixed m. p. 226—228°.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 8th,* 1955.]

Polypeptides. Part I. The Condensation-polymerisation of Some Polyglycine Esters and Azides.

By H. N. RYDON and P. W. G. SMITH.

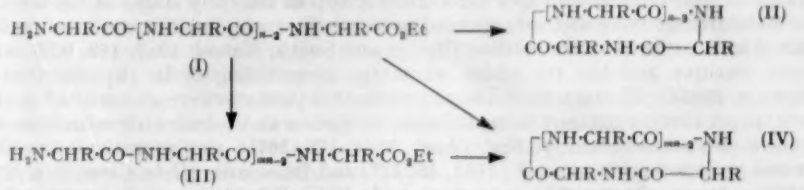
[Reprint Order No. 6225.]

The condensation-polymerisation of the ethyl esters of the series of polyglycines from glycylglycine to pentaglycylglycine has been studied. In the solid state, the di- and the tri-peptide polymerise much more readily than the others, polymerising completely at temperatures which bring about little or no polymerisation of the higher peptide esters. In *m*-cresol solution stepwise degradation occurs, pairs of glycine residues being split off as piperazine-2 : 5-dione.

The derived peptide azides polymerise in aqueous solution with the formation of polyglycines of high molecular weight.

THE condensation-polymerisation of esters, and other derivatives, of peptides can give rise to both open-chain and cyclic products; thus, intramolecular condensation-polymerisation of the peptide ester (I) would lead to the cyclic peptide (II) while the corresponding

intermolecular reaction could give rise to both the open-chain peptides (III) and the cyclic peptides (IV). The proportions in which these products are formed will depend on both



the length and the conformation of the peptide chain in both the original peptide (I) and its linear polymers (III), these conformations being, in turn, dependent on the nature of the side chain R and the stereochemical configuration of the individual amino-acid residues in (I). The three controllable structural variations in (I) which must be taken into account in any general study of the reaction are thus (*a*) the nature of R, (*b*) the stereochemical configuration of the amino-acid residues, and (*c*) the value of *n*. In order to simplify matters in this initial study by eliminating (*a*) and (*b*), we chose to work with polyglycine esters (I; R = H); values of *n* up to 6 appeared sufficient in the light of both the known influence of chain-length on the yields of macrocyclic carbon rings from open-chain compounds and the views of Pauling, Corey, and Branson (*Proc. Nat. Acad. Sci.*, 1951, **37**, 206) on the coiling of peptide chains.

Dipeptide esters are known to yield piperazine-2 : 5-diones readily by intramolecular condensation, (I) ⟶ (II); thus, Fischer and Fourneau (*Ber.*, 1901, **34**, 2868) found that piperazine-2 : 5-dione (II; $n = 2$), was rapidly formed at room temperature in aqueous solutions of glycylglycine ethyl ester (I; $n = 2$), although the action of heat on the ester in the absence of solvent yielded, in addition, a small amount of a product giving a positive biuret reaction; dipeptide esters readily cyclise to piperazine-2 : 5-diones on treatment with alcoholic ammonia (Fischer, *Ber.*, 1906, **39**, 467, 2893; Fischer and Reif, *Annalen*, 1908, **363**, 118; Butenandt, Karlson, and Zillig, *Z. physiol. Chem.*, 1951, **288**, 279). Tripeptide esters, on the other hand, appear to undergo linear polymerisation, (I) ⟶ (III) (for a review, see Katchalski, *Adv. Protein Chem.*, 1950, **6**, 123). The polymerisation of diglycylglycine methyl ester was first studied by Fischer (*Ber.*, 1906, **39**, 471), who obtained 76% of the hexapeptide ester, together with some water-insoluble material considered to be the dodecapeptide ester; this polymerisation has been studied in detail by Pacsu and Wilson (*J. Org. Chem.*, 1942, **7**, 117), who concluded, on the basis of methoxyl analyses, that stepwise dimerisation occurred wth the formation of peptide esters such as (III) with $n = 6$, 12, 24, 48, and 96. The literature on the polymerisation of triglycylglycine esters is conflicting; Curtius (*Ber.*, 1904, **37**, 1300) reported that the methyl ester, on being heated, yielded a water-insoluble product, formulated as "octaglycine anhydride," *i.e.* (IV; R = H; $n = 4$; $m = 2$), but Fischer (*Ber.*, 1906, **39**, 2927) could not detect any polymerisation under similar conditions. While our work was in progress, Sluyterman and Veenendaal (*Rec. Trav. chim.*, 1952, **71**, 137) re-investigated this reaction; at 100°, a prolonged induction period was followed by migration of methyl from oxygen to nitrogen with the formation of *N*-methylglycyldiglycylglycine, Me·NH·CH_2·CO·[NH·CH_2·CO]$_2$·NH·CH_2·CO_2H, *NN*-dimethylglycyldiglycylglycine, Me_2N·CH_2·CO·[NH·CH_2·CO]$_2$·NH·CH_2·CO_2H, and some triglycylglycine; at higher temperatures condensation-polymerisation occurred, with the formation of polyglycine esters (Sluyterman and Kooistra, *ibid.*, p. 277). More recently, however, Brockmann and Musso (*Chem. Ber.*, 1954, **87**, 581) observed no change on heating triglycylglycine methyl ester at 125° for 4 days, although decomposition, with the formation of the free tetrapeptide and other (unidentified) products, was observed at higher temperatures.

In this paper we describe the polymerisation, alone and in solvents, of the series of polyglycine ethyl esters ranging from glycylglycine ethyl ester (I; R = H; $n = 2$) to pentaglycylglycine ethyl ester, (I; R = H; $n = 6$). With the exception of the first-mentioned, these peptide esters were all prepared by the thiothiazolidone method of Cook

and Levy (*J.*, 1950, **646**); it was later found more convenient to prepare pentaglycylglycine ethyl ester by heating diglycylglycine ethyl ester. The polymerisation products were investigated qualitatively by paper chromatography; in the early stages of the work the usual ninhydrin spraying method was used to locate the spots, but this was later replaced by the chlorine–starch–iodide method (Rydon and Smith, *Nature*, 1952, **169**, 922), which is more sensitive and has the added advantage of revealing cyclic peptides (but see footnote, p. 2545). In many cases the polymerisation products were also studied quantitatively, paper chromatography being followed by elution and colorimetric estimation with ninhydrin (Moore and Stein, *J. Biol. Chem.*, 1948, **176**, 367); similar methods have been described by Fowden (*Biochem. J.*, 1951, **48**, 327) and Boissonnas (*Helv. Chim. Acta*, 1950, **33**, 1975). It was also possible, by elution, hydrolysis, and colorimetric estimation of the glycine so produced, to obtain an independent check on the chain-lengths of the products, which could also be inferred from the R_F values. In certain cases molecular weights were estimated colorimetrically by using the *N*-2 : 4-dinitrophenyl derivatives; details of the method are given in the Experimental section.

The results of the experiments in which the peptide esters were heated *in vacuo* in the solid state are summarised in Table 1; only the di- and the tri-peptide ester underwent appreciable reaction, the others being recovered largely unchanged. The formation of small amounts of free peptide is no doubt due to hydrolysis owing to the presence, in materials dried *in vacuo* at room temperature, of small amounts of tenaciously held adsorbed water (cf. Mellon, Korn, and Hoover, *J. Amer. Chem. Soc.*, 1947, **69**, 827; 1948, **70**, 3040).

Glycylglycine ethyl ester (I; R = H; $n = 2$) yielded piperazine-2 : 5-dione (II; R = H; $n = 2$) and triglycylglycine ethyl ester (III; R = H; $m = 2$; $n = 2$) as the sole products, there being no trace of higher polymers; this is borne out by the results of heating the tetrapeptide ester itself. Clearly, triglycylglycine ethyl ester does not react under these conditions with piperazine-2 : 5-dione, although the latter has been shown to react with glycine peptides in aqueous solution (Meggy, *J.*, 1953, 851); this result renders unlikely the suggestion (Carothers, *Chem. Rev.*, 1931, **8**, 389) that piperazine-2 : 5-dione is an intermediate in the thermal polymerisation of glycine.

Diglycylglycine ethyl ester (I; R = H; $n = 3$) yielded almost exclusively the hexapeptide ester (III; R = H; $m = 2$; $n = 3$) and this reaction is convenient for preparative purposes; a small amount of the nonapeptide ester (III; R = H; $m = 3$; $n = 3$) was

TABLE 1. *Products formed by heating polyglycine esters.*

Peptide ester *	Temp. and time of heating	Products
G_3Et	78° (20 hrs.)	G_3Et (25%) †; G_4Et (25%); piperazine-2 : 5-dione (50%).
	Room temp. (18 months)	G_4Et; piperazine-2 : 5-dione.
G_3Et	135° (12 hrs.)	G_3Et (83%); G_9Et (9%); higher polymers (trace).
	105° (1 month)	G_4Et; high polymer (main product).
G_3Me	108° (20 hrs.)	G_3Me; G_9Me; higher polymers.
	105° (1 month)	High polymers.
G_4Et	135° (12 hrs.)	G_4Et (83%); G_4H (9%).
	124° (9 hrs.) + 184° (7 hrs.)	G_4Et; G_4H; piperazine-2 : 5-dione (3%).
G_5Et	124° (17·5 hrs.)	G_5Et (86%); G_5H (trace).
	163° (17 hrs.)	G_5Et (80%); G_5H (4%).
G_6Et	124° (17 hrs.)	G_6Et; higher polymers (trace); G_9H (trace).
	163° (37 hrs.)	G_6Et; higher polymers (trace); G_6H (trace).

* In this Table, and elsewhere, G_nEt denotes (I; R = H; $n = n$), G_nMe the corresponding methyl ester, and G_nH the corresponding free peptide.
† Sublimed unchanged.

also formed. Ethyl esters of amino-acids are known to polymerise less readily than methyl esters (Abderhalden and Suzuki, *Z. physiol. Chem.*, 1928, **176**, 101; Frankel and Katchalski, *J. Amer. Chem. Soc.*, 1942, **64**, 2264) and we have observed the same difference with peptide esters; thus, diglycylglycine ethyl ester, sealed *in vacuo* over silica gel and heated at 105° for a month, yielded a product containing a considerable amount of the hexapeptide ester, whereas diglycylglycine methyl ester, treated similarly, yielded a water-insoluble polymer

which did not move from the starting-line on paper chromatography. Our results with the tri- and the hexa-peptide ethyl ester are notably different from those obtained by Pacsu and Wilson (*loc. cit.*) with the methyl esters; however, these authors relied solely on methoxyl analyses of the products, and the methyl migration observed by Sluyterman and Veenendaal (*loc. cit.*) in the case of the tetrapeptide methyl ester renders their interpretation of their results of doubtful significance.

In none of our experiments was there evidence of the formation of cyclic peptides (other than piperazine-2 : 5-dione); this suggests that these esters have the fully extended β-conformation which has been established for polyglycine by *X*-ray crystallographic methods (Meyer and Go, *Helv. Chim. Acta*, 1934, **17**, 1488; Astbury, Dalgleish, Darmon, and Sutherland, *Nature*, 1948, **162**, 596). The observed restriction of linear polymerisation to the di- and the tri-peptide ester in these solid-state reactions is no doubt due to a favourable orientation of the molecules within the crystal lattice in these two cases.

The results of heating 5% solutions of the peptide esters in *m*-cresol are summarised in Table 2. In every case piperazine-2 : 5-dione was a major component of the products and

TABLE 2. *Products formed from polyglycine ethyl esters at* 100° *in* 5% *solution in* m-*cresol.*

Peptide ester	Period of heating (hr.)	G_2Et	G_3Et	G_4Et	G_5Et	G_6Et	Higher polymers	Piperazine-2 : 5-dione
G_2Et ...	96	Trace	—	Trace	Trace	Trace	—	—	++
G_3Et ...	165	Trace	Trace	—	Trace	—	—	—	++
G_5Et ...	192	Trace	—	++	Trace	++	Trace	Trace	++
G_6Et ...	216	—	+	Trace	++	Trace	++	+	++

the results show clearly that, under these conditions, the peptide esters undergo degradation by the stepwise removal of pairs of glycine residues from the amino-end of the molecule, thus:

$$H_2N{\cdot}CH_2{\cdot}CO{\cdot}[NH{\cdot}CH_2{\cdot}CO]_{n-2}{\cdot}NH{\cdot}CH_2{\cdot}CO_2Et \longrightarrow$$

$$HN\begin{cases}CO{-}CH_2\\ CH_2{-}CO\end{cases}NH + + H_2N{\cdot}CH_2{\cdot}CO{\cdot}[NH{\cdot}CH_2{\cdot}CO]_{n-4}{\cdot}NH{\cdot}CH_2{\cdot}CO_2Et$$

A similar degradation of certain tripeptides on being heated in β-naphthol has been observed by Lichtenstein (*J. Amer. Chem. Soc.*, 1938, **60**, 560). This type of degradation may well be responsible for the formation of dioxopiperazines by the mild hydrolysis of certain proteins (cf., *e.g.*, Abderhalden, *Z. physiol. Chem.*, 1923, **128**, 119; Abderhalden and Komm, *ibid.*, 1924, **132**, 1). This mechanism should lead exclusively to odd peptide esters from odd peptide esters and to even peptide esters from even peptide esters. The formation of traces of even from odd peptide esters (G_4Et from G_3Et; G_4Et and G_6Et from G_5Et) is no doubt to be ascribed to direct polymerisation of the glycine ethyl ester which is the end product of the degradation of any odd peptide ester by the above route. The formation of traces of odd peptide esters from even (G_3Et and G_5Et from G_6Et) is, however, anomalous; a possible mechanism for their formation involves the removal of sets of three glycine residues as *cyclo*triglycine, but no trace of such a product could be detected in the reaction mixtures.* In the case of the penta- and the hexa-peptide ester polymerisation accompanied the degradation but no evidence could be obtained for the formation of cyclic peptides, other than piperazine-2 : 5-dione, although the possibility of the presence of small amounts of such products cannot be excluded.

Magee and Hofmann (*J. Amer. Chem. Soc.*, 1949, **71**, 1515) obtained a polyglycine by the polymerisation of diglycylglycine azide in aqueous solution and this reaction, carried out at high dilution, has very recently been used by Sheehan and Richardson (*ibid.*, 1954, **76**,

* The assumption that cyclic peptides would be revealed on chromatograms by the chlorination method was based on the positive reaction given by piperazine-2 : 5-dione (Rydon and Smith, *loc. cit.*). It has recently been found by one of us (P. W. G. S.) that cyclic tripeptides do not give the reaction at all readily; *cyclo*triglycine, if present in these reaction mixtures, would, therefore, probably not have been detected.

6329) for the preparation of *cyclo*triglycine (II; R = H; $n = 3$); we have made a preliminary investigation of the applicability of this reaction to higher peptide azides. The crude hydrazides prepared from di-, tri-, and tetra-glycylglycine ethyl ester were treated at 0° with aqueous nitrous acid; basification of the resulting solutions of the azides with sodium hydroxide resulted in every case in the precipitation of polyglycine. The products from the tri- and the tetra-peptide azide were insoluble, white, granular solids, similar to the polyglycine described by Magee and Hofmann (*loc. cit.*); that from the pentapeptide azide was a hard translucent solid and probably a higher polymer than the others. There is no doubt that the reaction is a general one, suitable for the preparation of polypeptides of high molecular weight (and probably also of *cyclo*peptides) containing repeating units made up of amino-acid residues with a pre-determined arrangement.

Experimental

Preparations.

Polyglycine Esters.—These were prepared and stored as their hydrochlorides (chromatographically pure) which were converted into the free esters immediately before use.

Glycylglycine ethyl ester. The hydrochloride, m. p. 181° (Schott, Larkin, Rockland, and Dunn, *J. Org. Chem.*, **1947**, **12**, 490), was converted into the free ester, m. p. 85—86°, in 74% yield by Fischer and Fourneau's method (*loc. cit.*).

Diglycylglycine ethyl ester. The hydrochloride, m. p. 215—216° (decomp.), was prepared in 25-g. batches in 82% yield by Cook and Levy's method (*loc. cit.*). This hydrochloride (1·5 g.) was suspended in ethanol (15 ml.) and cooled to 0° while ethanolic sodium ethoxide (from sodium, 135 mg., and ethanol, 4·3 ml.) was added dropwise with shaking; the product was evaporated to dryness at 30° under reduced pressure and the solid residue extracted with chloroform (3 × 5 ml.) at 40°. Addition of dry ether to the cooled, filtered extract precipitated the ester (900 mg., 70%), m. p. 107° (in bath at 102°).

Diglycylglycine methyl ester. 2-Thiothiazolid-5-one (2·5 g.) (Cook and Levy, *loc. cit.*; Pollock, Thesis, London, **1949**) was added to glycylglycine methyl ester hydrochloride (3·5 g.) in methanol (25 ml.) and triethylamine (3·8 g.). Acidification with methanolic hydrogen chloride precipitated the ester hydrochloride (3·8 g., 82%), m. p. 197° after recrystallisation from methanol. The free ester, m. p. 110° (in bath at 108°), was liberated, in 64% yield, by treatment with methanolic sodium methoxide as described by Pacsu and Wilson (*loc. cit.*).

Triglycylglycine ethyl ester. The hydrochloride, m. p. 212° (decomp.), was prepared in 84% yield by Cook and Levy's method (*loc. cit.*). This compound (2 g.), in water (5 ml.), was treated dropwise, with shaking, at 0° with triethylamine (0·8 g.). After 5 min., the semisolid mass was diluted with ethanol (10 ml.), filtered, and washed with ethanol; after trituration with more ethanol (10 ml.), the ester (1·3 g., 74%), no definite m. p., was dried *in vacuo* over silica gel.

Tetraglycylglycine ethyl ester. The hydrochloride, m. p. 233—234° (decomp.), prepared in 78% yield by Cook and Levy's method (*loc. cit.*), was converted into the free ester (78% yield) as described for the tetrapeptide ester.

Pentaglycylglycine ethyl ester. (*a*) Tetraglycylglycine ethyl ester hydrochloride (2 g.), in water (12·5 ml.), was treated with triethylamine (1·1 g.) in ethanol (17·5 ml.). A suspension of 2-thiothiazolid-5-one (0·74 g.) in ethanol (25 ml.) was immediately added and the mixture vigorously shaken for 15 min., most of the solid dissolving. 5N-Ethanolic hydrogen chloride (2·5 ml.) was added and the solution cooled to 0°. The solid which separated on scratching was recrystallised (charcoal) from aqueous ethanol containing a little hydrogen chloride, affording *pentaglycylglycine ethyl ester hydrochloride* (0·8 g., 35%), m. p. 239—240° (decomp.) (Found: C, 39·0; H, 6·0; OEt, 9·7. $C_{14}H_{25}O_7N_6Cl$ requires C, 39·6; H, 5·9; OEt, 10·6%). This hydrochloride (800 mg.), in warm water (4 ml.), was treated with triethylamine (200 mg.); ethanol (10 ml.) was added and the precipitate isolated by centrifugation, washed thrice with ethanol, and dried *in vacuo* over phosphoric oxide. The free *ester* (660 mg., 90%) was an amorphous solid with no definite m. p. (Found: OEt, 10·9. $C_{14}H_{24}O_7N_6$ requires OEt, 11·6%).

(*b*) Diglycylglycine ethyl ester (14 g.; in two batches) was heated at 130°/1 × 10^{-3} mm. for 12 hr. The product was warmed with 2N-hydrochloric acid and diluted with water (60 ml.); some yellow gelatinous insoluble matter was removed by filtration, after addition of charcoal and Supercel, and the filtrate diluted with ethanol (500 ml.) and kept at 0° overnight. One further recrystallisation from aqueous ethanol yielded the pure ester hydrochloride (8 g., 58%), m. p. 250° (decomp.) (Found: C, 39·7; H, 6·2%).

2 : 4-*Dinitrophenyl Derivatives*.—The following were prepared by shaking the peptide or peptide ester (2·5 mmole), in water (5 ml.) containing sodium hydrogen carbonate (5 mmole), with 1-fluoro-2 : 4-dinitrobenzene (2·75 mmole) in ethanol (10 ml.). Derivatives, as follows, of the esters crystallised directly from the reaction mixture; those of the free peptides were precipitated by acidification of the concentrated reaction mixture after extraction with ether.

N-2 : 4-*Dinitrophenylglycylglycine hemihydrate*, plates, m. p. 197° (decomp.), from aqueous methanol (Found : C, 38·9, 39·0; H, 3·9, 3·7; N, 17·3, 17·9. $C_{10}H_{10}O_7N_4,\frac{1}{2}H_2O$ requires C, 39·1; H, 3·6; N, 18·2%). N-2 : 4-*Dinitrophenylglycylglycylglycine*, m. p. 206—207° (decomp.), from methanol (Found : C, 41·0; H, 3·4; N, 19·6. $C_{12}H_{13}O_8N_5$ requires C, 40·6; H, 3·7; N, 19·7%); *ethyl ester*, m. p. 190° (decomp.), from aqueous ethanol (Found : C, 44·0; H, 4·5; N, 18·0. $C_{14}H_{17}O_8N_5$ requires C, 43·9; H, 4·5; N, 18·3%). N-2 : 4-*Dinitrophenylglycyldiglycylglycine ethyl ester*, m. p. 218° (decomp.), from water or methanol (Found : C, 43·5; H, 4·4; N, 19·3. $C_{16}H_{20}O_9N_6$ requires C, 43·6; H, 4·6; N, 19·1%). N-2 : 4-*Dinitrophenylglycyltriglycylglycine ethyl ester*, needles, m. p. 234—235° (decomp.), from water (Found : C, 43·5; H, 4·7; N, 20·3. $C_{18}H_{22}O_{10}N_7$ requires C, 43·5; H, 4·6; N, 19·7%).

Analytical Methods.

Qualitative.—Peptide mixtures from the polymerisation experiments were chromatographed on Whatman No. 1 paper, *n*-butanol-pyridine–water (65 : 35 : 65) (upper phase) being used as the developing solvent; the spots were located by spraying with ninhydrin (0·1% in *n*-butanol) or by the chlorine–starch–iodide method (Rydon and Smith, *loc. cit.*). Typical R_F values for the various polyglycine esters, applied as their hydrochlorides, are :

Peptide ester	G_2Et	G_3Et	G_4Et	G_5Et	G_6Et
R_F	0·49	0·40	0·34	0·29	0·23

Quantitative.—The ninhydrin reagent used was the following modification of that of Moore and Stein (*loc. cit.*), which was found to be unstable on keeping. Solution A : Ninhydrin (2 g.), dissolved in redistilled, peroxide-free, ethylene glycol monomethyl ether (50 ml.) and citrate buffer (40 ml.; citric acid monohydrate, 21·008 g., in N-sodium hydroxide, 200 ml., made up to 500 ml. with water). Solution B : 0·8% hydrated stannous chloride in citrate buffer; stored under liquid paraffin. For use, solution B (1 ml.) was added to solution A (9 ml.); fresh reagent was made up at least monthly.

Nine 8·79-µl. drops of a solution of the material for analysis (each containing *ca.* 0·3 µmole of amino-nitrogen) were placed, by means of a Blodgett pipette (cf. Harkins and Anderson, *J. Amer. Chem. Soc.*, 1937, **59**, 2193) on a sheet of Whatman No. 1 paper (24 × 24 in.) marked in 9 vertical strips. After drying, the chromatogram was developed for 15—20 hr. with the upper phase of *n*-butanol–pyridine–water (65 : 35 : 65) in a cabinet saturated with vapour from the lower phase of this mixture. After the paper had dried overnight at 30°, the centre strip, carrying the chromatogram of the fifth spot, was cut out and examined qualitatively as described above. The peptide spots on the other strips were then located precisely by viewing them in ultraviolet light, using the sprayed strip as a guide. The peptide spots on strips 1, 3, 7, and 9 were cut out, allowing *ca.* 7 mm. clearance, and each paper disc was then pushed to the bottom of a test-tube (17 × 1·5 cm.), treated with the ninhydrin reagent (1 ml.), and heated for exactly 20 min. in a vigorously boiling water-bath. After cooling, the contents of the tube were diluted with 50% aqueous *n*-propyl alcohol (9·1 ml.). The colour density of the filtered solution was then determined, against a reagent blank, in a Spekker Photoelectric Absorptiometer, with the Ilford Spectrum Yellow-Green Filter, No. 605. After correction for adsorbed ammonia (see below), the amino-nitrogen content was read off from a reference curve constructed from standard solutions of the appropriate peptide ester; all the peptide esters gave identical reference curves, within the limits of experimental error; fresh reference curves were constructed for each new batch of ninhydrin.

The amino-nitrogen content of the original solution was determined directly, on standard 8·79-µl. drops, by the above method.

For the determination of the ammonia blank, which was minimised by working in an isolated room reserved for the purpose, the peptide spots on strips 2 and 8 were cut out and each disc placed in the centre compartment of a Conway dish (Conway, "Microdiffusion Analysis and Volumetric Error," Lockwood, London, 1939); the outer compartment of the dish contained the ninhydrin reagent (2 ml.). Saturated potassium carbonate solution (1 ml.) was added to the centre compartment and the dish lid immediately put in place and sealed with Vaseline. The

whole was rocked at room temperature for 5 hr., 1 ml. was removed from the outer compartment, and the colour developed and measured as described above, a blank similarly prepared being used.

The peptide spots on strips 4 and 6 were cut out similarly and subjected to extraction and hydrolysis. The apparatus consisted of a test-tube (20 × 3·5 cm.) to which a cold-finger condenser was attached by means of a ground-glass joint; just below the bottom of the condenser and 8 cm. from the bottom of the test-tube, a small funnel was supported by means of indentations in the tube wall; a small glass bead was placed in the tube to prevent bumping. The paper disc was folded between clean sheets of filter-paper and placed in the funnel; it was then moistened with water containing a little 2N-hydrochloric acid and pushed into position with a glass rod, which was finally washed down with water (2 ml.). Extraction was carried out at gentle reflux for 6 hr., after which the funnel and paper were removed. Concentrated hydrochloric acid (3 ml.) was added and the solution refluxed for a further 24 hr., after which it was evaporated to dryness overnight in a vacuum-desiccator over potassium hydroxide. The residue was dissolved in water (1 ml.), and aliquot parts (0·2 ml.) were pipetted into test-tubes (17 × 1·5 cm.). 1% Methanolic potassium hydroxide (0·2 ml.) was added to each tube and the contents were again evaporated to dryness in a vacuum-desiccator over phosphoric oxide (6 hr.). 1·25% Citric acid (0·2 ml.) and ninhydrin reagent (1 ml.) were added and the colour was developed as usual. After addition of 50% aqueous *n*-propyl alcohol (8·0 ml.) the colour density of the cooled solution was measured against a similarly prepared blank, and the glycine content determined by means of a reference curve. The glycine content of the original solution was similarly determined after hydrolysis of a standard drop with 20% (w/v) hydrochloric acid.

Colorimetric Determination of Molecular Weights of N-2 : 4-*Dinitrophenyl Derivatives.*—The colour densities of solutions of *N*-2 : 4-dniitrophenylglycylglycine, *N*-2 : 4-dinitrophenylglycylglycylglycine and its ethyl ester, *N*-2 : 4-dinitrophenylglycyldiglycylglycine ethyl ester, and *N*-2 : 4-dinitrophenylglycyltriglycylglycine ethyl ester in mixtures of formamide and 1% aqueous sodium hydrogen carbonate were determined by using the Spekker Photoelectric Absorptiometer and Ilford Spectrum Violet Filters, No. 601; the colour values for equimolar solutions were all the same, conforming to a curve drawn through the points :

Concn. (mmolar)	0·05	0·10	0·15	0·20
Spekker reading	0·133	0·250	0·350	0·442

Molecular weights of glycine peptides and peptide esters may thus be determined by treatment with 1-fluoro-2 : 4-dinitrobenzene in aqueous-ethanolic sodium hydrogen carbonate, as described on p. 2547, dissolution of a weighed amount of the resulting *N*-2 : 4-dinitrophenyl derivative in a known volume of a suitable mixture of formamide and 1% aqueous sodium hydrogen carbonate, and determination of the colour density. The reaction with fluorodinitrobenzene should be repeated until the washed derivative no longer gives a positive ninhydrin reaction. This method gave, for authentic pentaglycylglycine ethyl ester, *M*, 414 (Calc. for $C_{14}H_{24}O_7N_6$: *M*, 388).

Polymerisations.

Heat-polymerisation.—The freshly prepared esters were dried in a vacuum-desiccator over phosphoric oxide and then under a high vacuum (10^{-3}—10^{-4} mm.) at room temperature for 2—3 hr. They were then heated, in a suitable vapour-bath, at 10^{-3}—10^{-4} mm. for the times specified in Table 1. The details of a typical experiment (line 3 of Table 1) follow :

Diglycylglycine ethyl ester was heated at 135° (refluxing " Ethylcellosolve ") for 12 hr.; the loss in weight was 13·4% (Calc. for loss of 1 mol. of ethanol from 2 mols. of ester : 10·6%). The product (103·0 mg.) was dissolved in water (10 ml.) containing 2N-hydrochloric acid (0·2 ml.) and this solution was employed for analysis (p. 2547) with the following results

		Amino-N (μmole)	Glycine after hydrolysis (μmole)	Mean chain-length (glycine residues)
Total polymer		0·211	1·305	6·2
Isolated peptides	R_F 0·26	0·175 (83%)	1·100	6·3
	R_F 0·04	0·019 (9%)	0·162	8·5

The chlorine–starch–iodide method revealed a trace of material, R_F 0, in addition to the spots with R_F 0·26 and 0·04; this is probably higher polymer.

Polymerisation in m-*Cresol.*—(a) *Diglycylglycine ethyl ester.* This (500 mg.) was heated at 100° in *m*-cresol (10 ml.) in a sealed tube for 96 hr.; the amino-nitrogen content of the final

solution had fallen to about 40% of its original value. The solution was diluted with dry ether (400 ml.), and the precipitated buff solid collected; chromatography showed the major component (53%) of this solid to be piperazine-2 : 5-dione, the other components being G_3Et, G_4Et, G_5Et, and glycine. The ethereal filtrate was concentrated under reduced pressure; chromatography showed the presence of G_3Et, glycine ethyl ester, and piperazine-2 : 5-dione.

(b) *Triglycylglycine ethyl ester.* This (500 mg.), in *m*-cresol (10 ml.), was heated similarly for 165 hr.; the amino-nitrogen content of the final solution was about 40% of the original. Precipitation with ether (400 ml.) yielded a solid (300 mg.), containing 47% of piperazine-2 : 5-dione together with G_4Et, G_3Et, and glycine; chromatography of the ethereal filtrate revealed only a little glycine ethyl ester.

(c) *Tetraglycylglycine ethyl ester.* This (500 mg.) in *m*-cresol (10 ml.) was heated at 100° for 192 hr. in an evacuated sealed tube; the amino-nitrogen content of the final solution was about 70% of the original. Chromatography showed the presence of the products indicated in Table 2, together with a trace of glycine.

(d) *Pentaglycylglycine ethyl ester.* This (500 mg.) in *m*-cresol (10 ml.) was heated at 100° for 216 hr. in an evacuated sealed tube; the amino-nitrogen content of the final solution was about 70% of the original. Chromatography showed the presence of the products indicated in Table 2, together with a trace of glycine.

Polymerisation of Polyglycine Azides.—(a) *Diglycylglycine azide.* Diglycylglycine ethyl ester hydrochloride (2·5 g.), suspended in ethanol (20 ml.), was treated with hydrazine hydrate (0·75 g.). After 4 days at room temperature, the solid (1·9 g.) was filtered off. This crude hydrazide (1·5 g.) was dissolved in N-hydrochloric acid (16 ml.) and cooled to 0°; 25% aqueous sodium nitrite was added until an immediate positive starch–iodide reaction was obtained. After 5 min. at 0°, the solution was brought to pH 10 with 2N-sodium hydroxide; gas was evolved and a white precipitate formed, which was collected by filtration after being kept at room temperature overnight. The product (0·75 g.) was an amorphous granular solid, not completely soluble in water; it gave an orange-brown colour, rapidly changing to violet, when boiled with ninhydrin, and a positive biuret reaction; chromatography showed the presence of a little diglycylglycine and much polymer; acid hydrolysis yielded only glycine.

(b) *Triglycylglycine azide.* Triglycylglycine ethyl ester (0·5 g.) was triturated with hydrazine hydrate (0·3 g.); the excess of hydrazine was removed in a vacuum-desiccator over concentrated sulphuric acid. The crude ethanol-washed product (0·4 g.) was dissolved in 2N-hydrochloric acid, treated with sodium nitrite, and basified as described in (a). The product (0·3 g.) was a granular white powder, difficultly soluble in hot water; it gave a positive ninhydrin reaction; chromatography revealed only polymeric material; acid hydrolysis yielded only glycine.

(c) *Tetraglycylglycine azide.* Tetraglycylglycine ethyl ester hydrochloride (3·7 g.), suspended in ethanol (25 ml.), was treated with hydrazine hydrate (1 g.); after 3 days at room temperature, the crude hydrazide (3·8 g.) was filtered off. This compound (2·1 g.) was treated with nitrous acid and basified, as described in (a). The product (360 mg.) was a hard translucent ninhydrin-positive solid.

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Some 1 : 1-*Diphenylpropyl and* 9-*Phenyl*-9-*fluorenyl Peroxides.*

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By reactions which involve the intermediate formation of 1 : 1-diphenylpropyl or 9-phenyl-9-fluorenyl carbonium ions, the corresponding alcohols have been converted successively into the alkyl hydroperoxides and dialkyl peroxides. The xanthhydryl or triphenylmethyl derivatives of the hydroperoxides have been prepared, and the carbonium ions which are formed by ionisation of the alcohols or peroxides have been characterised by the formation of 1 : 1-diphenylpropyl and 9-phenyl-9-fluorenyl *p*-tolyl sulphone.

1 : 1-Diphenylpropyl hydroperoxide and di-(9-phenyl-9-fluorenyl) peroxide have been prepared by other workers by homolytic autoxidation reactions. These two alkyl groups powerfully release electrons and it would be expected that such compounds could also be prepared from the corresponding alcohols by reactions involving unimolecular alkyl–oxygen heterolysis (Davies, Foster, and White, *J.*, 1953, 1541; 1954, 2200; Davies, Foster, and Nery, *J.*, 1954, 2204). A study of some 1 : 1-diphenylpropyl and 9-phenyl-9-fluorenyl peroxides by these reactions has now confirmed the structures assigned to them.

1 : 1-Diphenylpropanol reacts with concentrated hydrogen peroxide in the presence of a trace of acid to form 1 : 1-diphenylpropyl hydroperoxide which, in formic acid solution, disproportionates into hydrogen peroxide and bis-1 : 1-diphenylpropyl peroxide. As a derivative diagnostic of the 1 : 1-diphenylpropyl cation, 1 : 1-diphenylpropyl *p*-tolyl sulphone has been obtained by the reaction of the alcohol with sodium toluene-*p*-sulphinate in 90% formic acid. The hydroperoxide has been characterised by its alkylation with triphenylmethanol and with xanthhydrol to form the corresponding unsymmetrical peroxides.

9-Phenylfluoren-9-ol with a m. p. between 107° and 109° has been prepared by a variety of reactions (for references, see Elsevier's "Encyclopaedia of Organic Chemistry," 1946, Vol. XIII, p. 64), but from the reaction between phenylmagnesium bromide and fluorenone Arcus and Coombs (*J.*, 1954, 3977) isolated the alcohol with m. p. 85° and concluded that the compound was dimorphic. By the same method we obtained the alcohol, m. p. 84°; it formed a 1 : 1 compound with dioxan, which at 100°/1 mm. lost dioxan and water forming di-(9-phenyl-9-fluorenyl) ether.

9-Phenylfluoren-9-ol reacts with hydrogen peroxide to form the hydroperoxide which in acetic–sulphuric acid disproportionates, or is alkylated by more of the alcohol, yielding di-(9-phenyl-9-fluorenyl) peroxide, m. p. 193°. Other workers (for references, see *op. cit.*, p. 74) have reported melting points of 193° and 204°. We have confirmed the structure of the peroxide by converting it into 9-phenyl-9-fluorenyl *p*-tolyl sulphone, identical with the product obtained from the similar reaction of 9-phenylfluoren-9-ol. The hydroperoxide has also been characterised by the preparation of 9-phenyl-9-fluorenyl xanthhydryl peroxide.

Experimental

1 : 1-*Diphenylpropanol.*—The Grignard reaction between phenylmagnesium bromide and propiophenone gave crude 1 : 1-diphenylpropanol, m. p. 90—94°, in 75% yield. Several recrystallisations from light petroleum gave the pure alcohol, m. p. 94—95°. Hell and Bauer (*Ber.*, 1903, **37**, 231) and Tolopko and Jurgjenko (*Doklady Akad. Nauk S.S.S.R.*, 1954, **94**, 207) report m. p. 94—95° for the compound obtained from ethylmagnesium iodide and benzophenone, but no yields. We found that this reaction gave only 7—11% of the alcohol, together with a large amount of the olefin, m. p. 47·5°. A solution of the alcohol (1·15 g.) in 90% formic acid (30 c.c.) was kept overnight, then poured on ice, and the solid which separated was recrystallised from light petroleum, yielding 1 : 1-diphenylprop-1-ene (0·85 g.), m. p. 47·5°, undepressed on mixture with the olefin obtained from the above Grignard reaction (Found : C, 92·5; H, 7·4. Calc. for $C_{15}H_{14}$: C, 92·7; H, 7·3%).

1 : 1-*Diphenylpropyl Hydroperoxide.*—A solution of 1 : 1-diphenylpropanol (1·0 g.) in the minimum of ether was shaken for 5 hr. with 90% hydrogen peroxide (5 c.c.) containing concentrated sulphuric acid (0·02 c.c.). The product was diluted with water, and the ethereal layer

separated and washed with aqueous sodium hydrogen carbonate and with water. Removal of the ether gave an oil with a slight phenolic odour. The oil solidified when washed with water, yielding 1 : 1-diphenylpropyl hydroperoxide (1·22 g.), m. p. 79·0—79·5° (from light petroleum) (Found : C, 78·6; H, 7·1. Calc. for $C_{15}H_{16}O_2$: C, 78·9; H, 7·1%). Ziegler and Herte (*Annalen*, 1942, **551**, 206), and Tolopko and Jurgjenko (*loc. cit.*), report m. p. 81—82° and 80° respectively.

Bis-1 : 1-*diphenylpropyl Peroxide.*—1 : 1-Diphenylpropyl hydroperoxide (0·56 g.) was suspended in 90% formic acid (30 c.c.). Next day the precipitate was filtered off and recrystallised twice from light petroleum, yielding *di*-(1 : 1-*diphenylpropyl*) *peroxide* (76 mg.), m. p. 140—140·5° (Found : C, 85·0; H, 7·3. $C_{30}H_{30}O_2$ requires C, 85·0; H, 7·0%).

1 : 1-*Diphenylpropyl Xanthhydryl Peroxide.*—The hydroperoxide (0·53 g.), in chloroform (9 c.c.), was added to xanthhydrol (0·44 g.) in acetic acid (20 c.c.). Next day the solution was poured on ice, yielding 1 : 1-*diphenylpropyl xanthhydryl peroxide*, m. p. 86—87° (from light petroleum) (Found : C, 81·9; H, 5·7. $C_{28}H_{24}O_3$ requires C, 82·3; H, 5·9%).

1 : 1-*Diphenylpropyl Triphenylmethyl Peroxide.*—A mixture of the hydroperoxide (0·47 g.) in chloroform (8 c.c.), and triphenylmethanol (0·62 g.) in acetic acid (10 c.c.) containing sulphuric acid (1·0 c.c.), similarly yielded 1 : 1-*diphenylpropyl triphenylmethyl peroxide* (0·3 g.; from light petroleum), m. p. (rapid heating) 151—160°, (slow heating) 150—152° (Found : C, 86·4; H, 6·4. $C_{34}H_{30}O_2$ requires C, 86·8; H, 6·4%).

1 : 1-*Diphenylpropyl* p-*Tolyl Sulphone.*—A suspension of the alcohol (1·49 g.) in a solution of sodium toluene-p-sulphinate (1·27 g.) in 90% formic acid (30 c.c.) was kept for 1 day, then poured on ice, yielding 1 : 1-*diphenylpropyl* p-*tolyl sulphone*, m. p. 118·5° (Found : C, 75·4; H, 6·5; S, 9·3, 9·4. $C_{22}H_{22}O_2S$ requires C, 75·4; H, 6·3; S, 9·2%). An attempt to prepare the same derivative under similar conditions from the hydroperoxide gave only 1 : 1-diphenylprop-1-ene.

9-*Phenylfluoren*-9-*ol.*—The alcohol was prepared (Ullmann and von Wurstemberger, *Ber.*, 1904, **37**, 73) from phenylmagnesium bromide and fluorenone. The complex formed was decomposed with ammonium chloride, giving the crude alcohol in 80% yield. Recrystallisation from ether–light petroleum gave rhombs, m. p. 75°, which lost solvent and attained constant weight during 30 min. at 120°. The resulting colourless melt solidified on cooling, to yield 9-phenylfluoren-9-ol, m. p. 84° (Found : C, 88·3; H, 5·6. Calc. for $C_{19}H_{14}O$: C, 88·4; H, 5·45%). Recrystallisation from dioxan yielded a complex, m. p. 104°, containing approx. 1 mol. of dioxan of solvation (Found, after some days in air : C, 81·2; H, 6·2. Calc. for $C_{19}H_{14}O,C_4H_8O_2$: C, 79·8; H, 6·4%). An attempt to remove the solvent from a freshly prepared specimen at 100°/0·1 mm. gave a change in weight corresponding to a loss of 1 mol. of dioxan and $\frac{1}{2}$ mol. of water, and yielded di-(9-phenyl-9-fluorenyl) ether, m. p. 235—236° (Found : loss, 28·1. Calc. : loss, 28·0 %). Gomberg (*J. Amer. Chem. Soc.*, 1913, **35**, 200) reports m. p. 232—233° for the ether.

9-*Phenyl*-9-*fluorenyl Hydroperoxide.*—A solution of 9-phenylfluoren-9-ol (2·0 g.) in ether was stirred for 5 hr. with 90% hydrogen peroxide (5 c.c.) containing sulphuric acid (0·10 c.c.). The ethereal layer yielded crude 9-*phenyl*-9-*fluorenyl hydroperoxide* (2·0 g., 94%) which was precipitated from acetic acid by water, then having m. p. 53—55° (Found : C, 83·5; H, 5·7. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%).

Di-(9-*phenyl*-9-*fluorenyl*) *Peroxide.*—(i) *By alkylation of the hydroperoxide with the alcohol.* The alcohol (0·47 g.) in acetic acid containing sulphuric acid (0·10 c.c.) was added to a solution of the hydroperoxide (0·51 g.) in ether. Next day the solid which had separated (0·23 g.) was filtered off and recrystallised from benzene, yielding the solvated peroxide. The benzene was removed during 2 hr. at 100°/1 mm., leaving the pure peroxide, m. p. 193° (decomp.) (Found : C, 88·4; H, 5·45. Calc. for $C_{38}H_{26}O_2$: C, 88·7; H, 5·1%).

(ii) *By dismutation of the hydroperoxide.* A solution of the hydroperoxide in acetic acid containing sulphuric acid, after 10 min. at 50°, was poured over crushed ice, yielding the peroxide, m. p. and mixed m. p. 193° (decomp.). The peroxide was also obtained from a similar reaction in aqueous acetic acid in the absence of added sulphuric acid, but the hydroperoxide was recovered from absolute acetic acid.

9-*Phenyl*-9-*fluorenyl Xanthhydryl Peroxide.*—A solution of the hydroperoxide (0·27 g.) and xanthhydrol (0·17 g.) in acetic acid, after 16 hr., yielded 9-*phenyl*-9-*fluorenyl xanthhydryl peroxide* as prisms (from light petroleum; 0·38 g.), m. p. 123° (Found : C, 84·2; H, 5·0. $C_{32}H_{22}O_3$ requires C, 84·5; H, 4·9%).

9-*Phenyl*-9-*fluorenyl* p-*Tolyl Sulphone.*—(i) *From the alcohol.* Addition of 9-phenylfluoren-9-ol (0·50 g.) in acetic acid (5 c.c.) to sodium toluene-*p*-sulphinate (0·34 g.) in acetic acid (5 c.c.) containing sulphuric acid (0·05 c.c.) gave an immediate precipitate. Next day this

solid (0·31 g.) was recrystallised from ethanol, yielding *9-phenyl-9-fluorenyl p-tolyl sulphone*, m. p. 208—209° (decomp.) (Found: C, 78·9; H, 5·3; S 7·9. $C_{26}H_{20}O_2S$ requires C, 78·8; H, 5·1; S, 8·1%).

(ii) *From the peroxide.* By a similar procedure di-(9-phenyl-9-fluorenyl) peroxide yielded the same sulphone, m. p. and mixed m. p. 208—209° (decomp.).

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Interaction between the Aromatic Chromophores in Polyphenyl Hydrocarbons.

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It is shown that electron interaction between the chromophores in the linear *m*- and *p*-polyphenyls can account for the main features of their electronic spectra. In the *para*-series the first intense absorption is due to an in-phase combination of γ- and β'-transitions in the individual chromophores, whilst in the *meta*-series it is the β-states which in the main give rise to the strong absorption. In both series the transition moment is in the longitudinal direction.

Conjugation between the chromophores has been ignored though this probably occurs to some extent in both series. It has previously been suggested that the different characteristics of the spectra of the two series are due to the presence of conjugation in the *para*- but not in the *meta*-series. It is demonstrated that this is probably a secondary effect and that the difference can be interpreted without reference to conjugation between the aromatic rings.

IT is interesting to investigate the interaction between individual chromophores of linear *m*- and *p*-polyphenyls, $C_6H_5{\cdot}[C_6H_4]_{n-2}{\cdot}C_6H_5$, because the two series show marked differences in their electronic spectra (Gillam and Hey, *J.*, 1939, 1170). The frequency of the first intense band in the *para*-series decreases steadily as the number of aromatic rings is increased, no limit having been reached with the first six members, which have been studied experimentally. On the other hand, in the *meta*-series there is virtually no change in the frequency of this band after diphenyl: it has been examined up to *m*-sedeciphenyl ($n = 16$). For both the *m*- and the *p*-polyphenyls the intensity of absorption increases as the series is ascended, being roughly proportional to the number of chromophores in the molecule.

These phenomena have been discussed in terms of the Hückel L.C.A.O. molecular-orbital theory (Dewar, *J.*, 1952, 3532). This theory relies for its simplicity on the assumption that the Hamiltonian for the system can be written as a sum of one-electron operators. Although the theory sometimes appears to be confirmed by experiment, it fails in general to account satisfactorily for any but the broadest features of molecular electronic spectra. In particular the Hückel theory predicts that the electronic states of a molecule R–S in which there is no conjugation between R and S, are equal in energy to the states of RH and SH. Any shift in the bands of the chromophores R and S when they are joined together has been taken to indicate conjugation between R and S, and hence a certain degree of coplanarity between adjacent rings.

Longuet-Higgins and Murrell (*Proc. Phys. Soc.*, in the press) have however shown that, when terms are included in the Hamiltonian which allow for the repulsion between electrons,

there can be appreciable interaction between the chromophores in a molecule even when there is no conjugation between them.

In this paper it will be shown how the main features of the spectra of the polyphenyls can be interpreted as due to repulsion between the π-electrons of adjacent rings without invoking significant conjugation between the aromatic rings.

Method.—It has been shown by Pople (*Proc. Roy. Soc.*, in the press) that, for a molecule having two or more chromophoric groups which are not conjugated together, the self-consistent molecular orbitals of the molecule are just those of the individual chromophores considered separately. The electronic states of such a molecule are of two kinds. There are those states which involve the excitation of an electron between two orbitals belonging to the same chromophoric group, and those which involve the transfer of an electron between molecular orbitals localized on different groups. The former are described as " locally excited " states, and the latter as " electron transfer " states.

Electron interaction has the effect of mixing the locally excited states of one chromophore with the locally excited states of all the others. There will be no mixing with any electron transfer states if there is no conjugation between the chromophores.

For the polyphenyls the locally excited states will correspond to the excited states of a benzene molecule. If the π-orbitals of benzene are written in their real forms, as follows :

$$\psi_6 = \sqrt{\tfrac{1}{6}}\{\phi_1 - \phi_2 + \phi_3 - \phi_4 + \phi_5 - \phi_6\}$$
$$\psi_5 = \sqrt{\tfrac{1}{12}}\{2\phi_1 - \phi_2 - \phi_3 + 2\phi_4 - \phi_5 - \phi_6\}$$
$$\psi_4 = \tfrac{1}{2}\{-\phi_2 + \phi_3 - \phi_5 + \phi_6\}$$
$$\psi_3 = \tfrac{1}{2}\{\phi_2 + \phi_3 - \phi_5 - \phi_6\}$$
$$\psi_2 = \sqrt{\tfrac{1}{12}}\{2\phi_1 + \phi_2 - \phi_3 - 2\phi_4 - \phi_5 + \phi_6\}$$
$$\psi_1 = \sqrt{\tfrac{1}{6}}\{\phi_1 + \phi_2 + \phi_3 + \phi_4 + \phi_5 + \phi_6\}$$

where ϕ_r are a set of orthogonal atomic-orbital functions, then the singly excited states of lowest energy are :

	Excitation energy (ev)
$\Psi_{\beta'} = \sqrt{\tfrac{1}{2}}(\chi_3^4 - \chi_2^5)$	6·74
$\Psi_{\beta} = \sqrt{\tfrac{1}{2}}(\chi_3^5 + \chi_2^4)$	6·74
$\Psi_{\gamma} = \sqrt{\tfrac{1}{2}}(\chi_3^4 + \chi_2^5)$	6·14
$\Psi_{\alpha} = \sqrt{\tfrac{1}{2}}(\chi_3^5 - \chi_2^4)$	4·88

where χ_k^l represents a configuration in which one electron has been excited from ψ_k to ψ_l.

The matrix element of the interaction between two configurations χ_k^l and χ_m^n obtained by exciting electrons within different chromophores is given by

$$\iint \chi_k^l H \chi_m^n \mathrm{d}\tau = 2\iint \psi_k(i)\psi_l(i)\frac{1}{r_{ij}}\psi_m(j)\psi_n(j)\mathrm{d}\tau_{ij}$$

According to Pariser and Parr (*J. Chem. Phys.*, 1953, **21**, 767) and Pople (*Trans. Faraday Soc.*, 1953, **49**, 1375), an approximation to this integral can be obtained by expanding the molecular orbitals in terms of atomic-orbital functions, neglecting all integrals except those of the form

$$\iint \phi_\mu^2(i)\frac{1}{r_{ij}}\phi_\nu^2(j)\mathrm{d}\tau_{ij}$$

Pople replaces these integrals by the interaction energy of point charges at the nuclei. The evaluation of the matrix elements of the interaction between the locally excited states therefore reduces to the evaluation of the interaction energy of point-charge distributions on the aromatic rings. These charge distributions for the four lowest energy states of

benzene are as shown. It is evident that the locally excited α-states will remain unaffected by electron interaction. In any case they give rise to weak transitions since in benzene the α-band is symmetry-forbidden.

It will now be shown how these locally excited states interact in the *m*- and the *p*-polyphenyl series.

p-*Polyphenyls.*—Since the γ- and the β′-state can be represented by charge distributions symmetrical about the longitudinal axis of the molecule, whilst the β states have a charge distribution antisymmetrical about this axis, there will be no mixing of the γ- and the β′-states with the β-states. Moreover, since we are interested in the lowest allowed transition, we can confine our attention to the γ- and the β′-states, since the β-states interact only weakly.

The locally excited γ- and β′-states will interact to give states of the form

$$\Psi = \sum_r a_r \Psi_\gamma + \sum_r b_r \Psi_{\beta' r}$$

the summations being over all the chromophores in the molecule. When all but nearest neighbour interactions are neglected, the coefficients a_r and b_r are obtained by solving the secular equations :

$$\left.\begin{aligned}(E_\gamma - E)a_r + H_{\gamma\gamma}(a_{r-1} + a_{r+1}) + H_{\gamma\beta'}(b_{r-1} + b_{r+1}) = 0\\ (E_{\beta'} - E)b_r + H_{\beta'\beta'}(b_{r-1} + b_{r+1}) + H_{\beta'\gamma}(a_{r-1} + a_{r+1}) = 0\end{aligned}\right\} \quad . \quad . \quad (1)$$

where H_{xy} is the interaction between the state Ψ_x of r and Ψ_y of $(r+1)$. For the *para*-series $H_{xy} = H_{yx}$. Equations (1) can be solved by taking the coefficients in periodic form, namely :

$$a_r = A \sin r\theta$$
$$b_r = B \sin r\theta$$

where $\theta = p\pi/(n+1)$. The secular equations then become :

$$\left.\begin{aligned}\{(E_\gamma - E)A + 2H_{\gamma\gamma}A \cos\theta + 2H_{\gamma\beta'}B \cos\theta\} \sin r\theta = 0\\ \{(E_{\beta'} - E)B + 2H_{\beta'\beta'}B \cos\theta + 2H_{\gamma\beta'}A \cos\theta\} \sin r\theta = 0\end{aligned}\right\} \quad . \quad . \quad (2)$$

and these are consistent if

$$\begin{vmatrix}(E_\gamma - E) + 2H_{\gamma\gamma}\cos\theta & 2H_{\gamma\beta'}\cos\theta\\ 2H_{\gamma\beta'}\cos\theta & (E_{\beta'} - E) + 2H_{\beta'\beta'}\cos\theta\end{vmatrix} = 0 \quad . \quad . \quad (3)$$

There will be a set of such determinants arising from the n distinct non-zero values of $\sin[p\pi/(n+1)]$. Of the $2n$ roots of these equations, that of lowest energy corresponds to $p = 1$, and is given by

$$E = \frac{E_\gamma + E_{\beta'}}{2} + (H_{\gamma\gamma} + H_{\beta'\beta'})\cos\frac{\pi}{n+1} - \tfrac{1}{2}\left\{\left(E_\gamma - E_{\beta'} + 2(H_{\gamma\gamma} - H_{\beta'\beta'})\cos\frac{\pi}{n+1}\right)^2 + 16H_{\gamma\beta'}{}^2\cos^2\frac{\pi}{n+1}\right\}^{\frac{1}{2}} \quad . \quad (4)$$

If all the aromatic rings are taken to have the geometry of benzene, with a bond length 1·39 Å, and the connecting bonds to be of length 1·46 Å, the matrix elements of the interaction have the values :

$$H_{\gamma\gamma} = -0{\cdot}20 \text{ ev}$$
$$H_{\beta'\beta'} = -0{\cdot}93 \text{ ev}$$
$$H_{\gamma\beta'} = 0{\cdot}28 \text{ ev}$$

The aromatic rings are assumed to lie in the same plane, but it was shown by Longuet-Higgins and Murrell (*loc. cit.*) that these matrix elements are almost independent of this assumption.

Table 1 gives the energies of the lowest allowed transitions calculated from equation (4), and compares then with the observed results. If second-neighbour interaction is included

TABLE 1. *Comparison of the observed and calculated energies of the lowest allowed transition in the* p-*polyphenyls* (Gillam and Hey, *J.*, 1939, 1170).

	Energy (ev)		Observed intensity		Energy (ev)		Observed intensity
n	obs.	calc.	(10^{-3} $\varepsilon_{max.}$)	*n*	obs.	calc.	(10^{-3} $\varepsilon_{max.}$)
2	4·93	5·58	18·3	5	4·00	4·86	62·5
3	4·43	5·18	25	6	3·90	4·79	>56
4	4·13	4·97	39	∞	—	4·62	—

the energy of *p*-terphenyl is lowered by 0·2 ev. Also it was shown by Longuet-Higgins and Murrell (*loc. cit.*) that, if conjugation is allowed for between the chromophores, the energy of the band in diphenyl is reduced by 0·36 ev. Both these effects explain why our calculated energies are consistently too high.

The lowest-energy band corresponds to an in-phase excitation of the γ- and the β′-state of each chromophore, and as such will be strongly allowed.

m-*Polyphenyls*.—The β-state of each ring may be taken to have a nodal plane perpendicular to the length of the molecule, and the transition dipoles of these states to be in the same direction. It is then found that the interaction elements between the β-states and the γ- and β′-states obey the relations :

$$H_{\gamma\beta} = -H_{\beta\gamma};\ H_{\beta'\beta} = -H_{\beta\beta'}$$

The excited states for the molecule must be expressed in the form :

$$\Psi = \sum_r a_r \Psi_{\gamma r} + \sum_r b_r \Psi_{\beta' r} + \sum_r c_r \Psi_{\beta r}$$

since there is interaction between all three types of state. If all interactions except those between nearest neighbours are again ignored, the coefficients a_r, b_r, and c_r are obtained by solving the following secular equations :

$$\left.\begin{aligned}
&(E_\gamma - E)a_r + H_{\gamma\gamma}(a_{r+1} + a_{r-1}) + H_{\gamma\beta'}(b_{r+1} + b_{r-1}) + H_{\gamma\beta}(c_{r+1} - c_{r-1}) = 0\\
&(E_{\beta'} - E)b_r + H_{\beta\beta'}(b_{r+1} + b_{r-1}) + H_{\gamma\beta'}(a_{r+1} + a_{r-1}) + H_{\beta'\beta}(c_{r+1} - c_{r-1}) = 0\\
&(E_\beta - E)c_r + H_{\beta\beta}(c_{r+1} + c_{r-1}) + H_{\beta\gamma}(a_{r+1} - a_{r-1}) + H_{\beta\beta'}(b_{r+1} - b_{r-1}) = 0
\end{aligned}\right\} \quad (5)$$

It is not possible to find an explicit general solution of equations (5) but a solution can be obtained for the infinite chain. In this case we can ignore end effects, and write :

$$\begin{aligned}
a_r &= A \sin r\theta,\\
b_r &= B \sin r\theta,\\
c_r &= C \cos r\theta
\end{aligned}$$

where $\theta = p\pi/(n+1)$. We find, as in the *para*-series, that for consistency it is necessary that

$$\begin{vmatrix}
(E_\gamma - E) + 2H_{\gamma\gamma}\cos\theta & 2H_{\gamma\beta'}\cos\theta & -2H_{\gamma\beta}\sin\theta\\
2H_{\gamma\beta'}\cos\theta & (E_{\beta'} - E) + 2H_{\beta'\beta'}\cos\theta & -2H_{\beta'\beta}\sin\theta\\
-2H_{\gamma\beta}\sin\theta & -2H_{\beta'\beta}\sin\theta & (E_\beta - E) + 2H_{\beta\beta}\cos\theta
\end{vmatrix} = 0$$

The interaction elements are as follows :

$$\begin{aligned}
H_{\gamma\gamma} &= 0{\cdot}20 \text{ ev} & H_{\beta\beta} &= -0{\cdot}61 \text{ ev}\\
H_{\beta'\beta'} &= -0{\cdot}05 \text{ ev} & H_{\gamma\beta} &= -0{\cdot}25 \text{ ev}\\
H_{\gamma\beta'} &= 0{\cdot}14 \text{ ev} & H_{\beta'\beta} &= -0{\cdot}58 \text{ ev}
\end{aligned}$$

The root of lowest energy will arise from $p = 1$, in which case $\cos \theta = 1$, $\sin \theta = 0$. The lowest-energy band for the infinite chain should therefore have an energy $E_\beta - 2H_{\beta\beta} = 5{\cdot}52$ ev. This band is seen to arise from an in-phase excitation of the β-bands of the aromatic chromophores. The energy of the strong absorption band of *m*-terphenyl has been calculated separately by considering only the effect of electron interaction between adjacent rings. It is found to be 5·46 ev.

These results are compared in Table 2 with the experimental values obtained by Gillam and Hey.

TABLE 2. *Comparison of the observed and the calculated energies of the lowest allowed transition in the* m-*polyphenyls.*

	Energy (e*V*)		Intensity		Energy (e*V*)		Intensity
n	obs.	calc.	(10^{-3} $\varepsilon_{max.}$)	*n*	obs.	calc.	(10^{-3} $\varepsilon_{max.}$)
2	4·93	5·58	18·3	13	4·90	—	252
3	4·93	5·46	44	14	4·90	—	283
9	4·90	—	184	15	4·88	—	309
10	4·90	—	213	16	4·86	—	320
11	4·90	—	215	∞	—	5·52	—
12	4·90	—	233				

Discussion.—We have shown above how electron interaction between the chromophores in the polyphenyls can account for the main features of their electronic spectra. In the *para*-series the lowest allowed transition arises from an in-phase excitation of the γ- and the β′-bands of the individual chromophores, whilst in the *meta*-series it is an in-phase excitation to the β-states which contributes the largest part of the absorption. In the *para*-series interaction between the chromophores is such as to give a slow convergence for the frequency of the band towards the limit reached by the infinite chain. In the *meta*-series, however, our calculations explain why there is little change in frequency after diphenyl. In both series the transition which gives rise to the strong absorption band has a moment in the longitudinal direction, which is why the intensity of the band increases as either series is ascended.

Our calculated energies are consistently greater than those observed both for the *meta*- and the *para*-series, but this is to be expected since we have neglected the effect both of electron interaction between non-nearest neighbours and of conjugation between the chromophores. These effects appear to be of secondary importance since the general features of the spectra are obtained without considering them.

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Electronic Spectra of Organic Molecules and their Interpretation. Part I. Effect of Terminal Methyl and Substituted Methyl Groups of Conjugated Systems on K*-Bands.*

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The effect of methyl and substituted methyl groups at the ends of conjugated systems A·CH_2·[CH:CH]$_n$·CH·A on the position of the corresponding *K*-bands is studied. The dependence of the energy of transition on the facility of the electron migration in one direction of the absorbing conjugated system is demonstrated. Structural modifications of a terminal group which increase its polarisability or the polarity of the absorbing system displace the *K*-band to longer wavelengths. Single bonds of substituted methyl groups (A·CH_2) participate in the electron migration of the transition and in favourable cases cause red-shifts comparable to those brought about by an additional conjugated double bond (A:CH). These results cannot be explained in terms of electromeric electron displacements or structures involving non-localised bonds, but are accounted for by inductomeric displacements of " localised " electrons.

The effect of substituents on the position of absorption bands in the electronic spectra of organic compounds is of considerable complexity, since it depends both on the location of the substituent within the absorbing system and on the type of the electronic transition involved, *i.e.*, the type of absorption band under consideration (for the classification of the bands above 2000 Å as *R*-, *K*-, and *B*(enzenoid)- bands, see Burawoy, *Ber.*, **1930**, **63**, 3155; 1931, **64**, 464, 1635; 1932, **65**, 941; *J.*, 1939, 1177; *Discuss. Faraday Soc.*, **1950**, **9**, 70).

The *K*-bands of comparatively high intensity ($\varepsilon > 5000$) are best understood. There is general agreement that qualitatively they are due to transitions involving electron migrations along (the axes of) conjugated systems such as (I) [cf., *e.g.*, Mulliken's N ⟶ V transitions (*J. Chem. Phys.*, **1935**, **3**, 522; 1939, **7**, 14, 21, 121, 339, 357, 395); Lewis and Calvin's class I oscillators (*Chem. Rev.*, 1939, **25**, 303); Burawoy, *loc. cit.*, **1950**]. As one of us has deduced empirically and supported by considerable evidence, the position of a *K*-band is determined by two factors: (i) the polarity of the absorbing system, *i.e.*, influences increasing its polarity (in the ground state) facilitate the electron migration, stabilise the excited state, and displace the *K*-band to longer wavelengths; (ii) the extension of the absorbing conjugated system or, as will be defined more precisely in this paper, the polarisability of the electrons of the terminal groups or atoms (I; A or B): the higher the polarisability, the greater the displacement to longer wavelengths.

(I) A·[CH:CH]$_n$·B ⟶

We have investigated the effect of methyl and substituted methyl groups as terminal groups A or B [in (I)] of certain conjugated systems on the position of the corresponding *K*-bands in order to derive information about the relative importance of these two factors, and also to test the justification or otherwise for the valency conception of hyperconjugation.

Methyl Group.—In Table 1 data showing the effect of terminal methyl groups of conjugated systems on the positions of the corresponding *K*-bands are reproduced. In the examples 1—5 the position of the *K*-band is determined by the facility of the electron migration along the absorbing system proceeding from the terminal methyl group as indicated in (II). The introduction of the *p*-methyl group is responsible for appreciable red-shifts due to the two factors mentioned, the increased polarity of the substituted system and the replacement of the terminal H–C electrons by the more strongly polarisable electron system of Me–C, both factors facilitating the electron migration (to the excited state). Similarly, the displacement to longer wavelengths due to the methyl group

TABLE 1. *Maxima of* K*-bands of compounds* p-$X{\cdot}C_6H_4{\cdot}H$ *and* p-$X{\cdot}C_6H_4{\cdot}Me$.

			p-$X{\cdot}C_6H_4{\cdot}H$		p-$X{\cdot}C_6H_4{\cdot}Me$		
No.	X	Solvent	λ (Å)	ε	λ (Å)	ε	Δλ
1	H *	H_2O	2035	7,400	2065	7,000	30
2	Ph	C_6H_{14}	2467	19,000	2513	19,100	46
3	COMe	C_6H_{14}	2387	12,500	2466	17,500	79
4	$CMe{:}\overset{+}{O}H$	H_2SO_4	2950	28,000	3113	30,000	163
5	NO:O	C_6H_{14}	2513	9,500	2645	10,000	132
6	p-$MeO{\cdot}C_6H_4$	C_6H_{14}	2595	21,500	2602	23,600	7
7	NH_2	EtOH	2344	8,000	2355	10,000	11
8	O^-	0·1N-NaOH	2345	11,000	2359	9,500	14

* Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714.

becomes greater with the increasing electron demand by the substituted system, *i.e.*, the increasing polarity of the Me–C bond. The red-shift is smallest in toluene and 4-methyldiphenyl, greater in 4-methylacetophenone and *p*-methylnitrobenzene, and most pronounced in the oxonium ion of 4-methylacetophenone.

(II) $Me{\cdot}C_6H_4{\cdot}X\text{-}p \longrightarrow$ (X = H, Ph, COMe, $CMe{:}\overset{+}{O}H$, NO:O)

(III) $Me{\cdot}C_6H_4{\cdot}X\text{-}p \longleftarrow$ (X = p-$MeO{\cdot}C_6H_4$, NH_2, O^-)

The effect of a *p*-methyl substituent on the *K*-bands of aniline, the phenoxide ion, and 4-methoxydiphenyl (nos. **6**—**8**) is different. The methyl group is now at the negative end of the absorbing system, *i.e.*, the electron migration determining the stability of the excited state proceeds into the methyl group as indicated in (III). The polarity of the substituted system and, thus, its polarisability in direction of the electron migration will be reduced (factor 1), which should cause displacement of the *K*-band to shorter wavelengths. On this, however, is superimposed a red-shift due to the replacement of the H–C electrons by the more strongly polarisable Me–C electrons (factor 2). The latter factor being greater, the overall result is a small displacement to longer wavelengths. In the examples **1**—**5**, factor 2 should be even more preponderant, since the polarity of the C_{Me}–C_{CO} bond suggests a stronger electronic polarisability towards the aromatic carbon atom.

α-Substituted p-*Nitrotoluene Derivatives.*—An investigation into the effect of substituents in terminal methyl groups on the position of a *K*-band affords additional evidence for its dependence on the direction of the electron migration and the reality of the twofold function of a terminal group of the absorbing system. The data for α-substituted *p*-nitrotoluene derivatives (Table 2) show that the *K*-band of *p*-nitrotoluene is displaced to *shorter* wavelengths as the electron-attracting power (inductive effect) of the α-substituents (IV; A) increases, *i.e.*, in the order $H < Br < Br_2 < Br_3$, $H < Cl < Cl_2 < Cl_3$, and $H < NH_2$ (in ethanol) $< OH < Cl < C{:}N < \overset{+}{N}H_3 < NO_2$.

(IV) $A{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO{:}O\text{-}p \longrightarrow$

The introduction of electron-withdrawing substituents into the methyl group reduces the polarity of the $A{:}CH_2$–C bond and, to a smaller degree, by inductive transfer, that of the other linkages of the absorbing system relative to the electron migration and, thus, is responsible for a hypsochromic shift of the *K*-band. The absorption maximum is in no case at shorter wavelengths than for nitrobenzene itself, although in many cases such as ω : *p*-dinitrotoluene, 4-nitrobenzyl cyanide, and the 4-nitrobenzylammonium ion (IV; A = NO_2, $C{:}N$, $\overset{+}{N}H_3$) the substituent $A{\cdot}CH_2$ is more strongly electron-attracting than is the hydrogen atom. This illustrates the important contribution of the increased polarisability of the C–C electrons (factor 2) to the red-shift caused by the methyl group, which only in the case of ω : *p*-dinitrotoluene is just cancelled by the hypsochromic effect due to the reduced polarity of the system (factor 1).

However, it will be noticed that the *K*-bands of 4-nitrobenzylamine (in hexane), 4-nitrobenzyl iodide, and 4-nitrodiphenylmethane appear at wavelengths slightly longer

than that of *p*-nitrotoluene, in spite of the electron-withdrawing character of the corresponding substituents which is illustrated by the dissociation constants of acetic acid, iodoacetic acid, and phenylacetic acid (Table 2). Moreover, the displacement to shorter

TABLE 2. *Maxima of* K-*bands of compounds* p-$NO_2 \cdot C_6H_4 \cdot X$.

	n-Hexane			Ethanol			10^5K of
X	λ (Å)	ε	Δ (X-Me)	λ (Å)	ε	Δ(X-Me)	$HO_2C \cdot X$ *
H	2513	9,500	—	2595	9,500	—	17·1
$CH_2 \cdot NO_2$	2513	12,500	−132	—	—	—	—
$CH_2 \cdot \overset{+}{N}H_3$	—	—	—	2620	11,000	−106	—
$CH_2 \cdot CN$	2547	11,000	− 98	—	—	—	342·0
CCl_3	2553	14,600	− 92	—	—	—	20000·0
$CHCl_2$	2560	14,500	− 85	—	—	—	5000·0
CH_2Cl	2581	12,500	− 64	2650	12,000	− 76	155·0
$CH_2 \cdot OH$	2610	12,000	− 35	2705	10,000	− 21	15·0
CBr_3	2632	16,500	− 13	—	—	—	—
$CHBr_2$	2635	17,000	− 10	—	—	—	—
CH_2Br	2641	15,000	− 4	2705	12,000	− 21	138·0
$CH_2 \cdot NH_2$	2651	12,500	+ 6	2715	10,000	− 11	—
CH_3	2645	10,000	0	2726	10,000	0	1·75
CH_2I	2649	15,000	+ 4	—	—	—	75·0
CH_2Ph	2660	13,500	+ 15	—	—	—	4·88

* Dippy, *Chem. Rev.*, 1939, **35**, 151; La Mer and Downes, *J. Amer. Chem. Soc.*, 1933, **55**, 1840; Ives and Sames, *J.*, 1943, 513; Walden, *Z. phys. Chem.*, 1892, **10**, 638; Ostwald, *ibid.*, 1889, **3**, 418.

wavelengths caused by the introduction of bromine atoms and, to a smaller degree, of chlorine atoms into *p*-nitrotoluene is also smaller than might have been expected. Braude (*J.*, 1949, 1902) has already pointed out that the inflexion corresponding to the *K*-band of diphenylmethane appears at longer wavelengths than the *K*-band of toluene and discussed it in terms of hyperconjugated structures (cf. also Bowden, Braude, and Jones, *J.*, 1946, 948; Bowden and Braude, *J.*, 1952, 1068).

These facts show that the α-substituents are not only responsible for a displacement of the *K*-band to shorter wavelengths by reducing the polarity of the absorbing system, but, like groups directly attached to the double bond of a conjugated system, can make appreciable bathochromic contributions due to the greater polarisability of the A–CH_2 electrons. The latter effect, normally only small, cannot be neglected, if the electronic polarisability of the new substituent is high as in C–I, C–Br or C–Ph. This indicates that the electrons of the A–C bonds participate in the electron migration to the excited state (cf. also below).

It is noteworthy that the displacements to shorter wavelengths on introduction of Cl, Br, or NH_2 are *greater* in ethanol than in hexane. This should be attributed to a smaller increase of polarity of the corresponding (less polar) 4-nitrobenzyl derivatives on change to the solvent of higher dielectric constant, and possibly to external hydrogen-bond formation by these substituents (cf. Ungnade, *J. Amer. Chem. Soc.*, 1953, **75**, 432). Hydrogen-bond formation in ethanol should also account for the *smaller* shift to shorter wavelengths of 4-nitrobenzyl alcohol, the latter serving now as hydrogen donor (cf. Burawoy and Chamberlain, *J.*, 1952, 2310).

α-*Substituted* p-*Toluidine Derivatives.*—These conclusions are convincingly confirmed by the effect of substituted methyl groups at the " receiving " end of the electron migration. The maxima of the *K*-bands of α-substituted *p*-toluidine derivatives (V) are shown in Table 3. In these compounds the introduction of electron-withdrawing substituents (B) into the methyl group increases the polarity of the C–CH_2B bond and, by inductive transfer, that of the other linkages of the absorbing system relative to the direction of the electron migration. This results in displacements of the *K*-band of *p*-toluidine to *longer* wavelengths, increasing in the order of the electron-attracting power of the substituents, *i.e.*, $H < Ph < NH_2 \sim OH < CN < NH_3^+$. Again, the rather high red-shift of the *K*-band of 4-aminobenzylamine (B = NH_2) and, in particular, of 4-aminodiphenylmethane (B = Ph) is accounted for by the comparatively high polarisability of the electron system of the C–NH_2 and C–Ph groups. In contrast to the cases of 4-nitrobenzylamine and 4-nitrodiphenylmethane, this contribution here enhances the red-shift due to the increased

polarity of the absorbing system. Unfortunately, the instability of α-halogeno-*p*-toluidines precluded the extension of this investigation to C–Hal bonds.

(V) p-$NH_2 \cdot C_6H_4 \cdot CH_2 \cdot B$ ⟶ p-$MeO \cdot C_6H_4 \cdot C_6H_4 \cdot CH_2 \cdot B$-$p$ (VI)

α-Substituted 4-Methoxy-4′-methyldiphenyl Derivatives.—We have, therefore, investigated the α-substituted derivatives of 4-methoxy-4′-methyldiphenyl, in which the electron migration responsible for the position of the *K*-band again involves an electron recession into the methyl group (VI; B = H). Maxima of the *K*-bands of the various compounds are reproduced in Table 3.

TABLE 3. *Maxima of* K*-bands.*

	p-$H_2N \cdot C_6H_4 \cdot X$ in ethanol			p-$MeO \cdot C_6H_4 \cdot C_6H_4 \cdot X$-$p$ in hexane		
X	λ (Å)	ε	$\Delta_{(X-Me)}$	λ (Å)	ε	$\Delta_{(X-Me)}$
H	2344	8,000	—	2595	22,000	—
CH_3	2355	11,000	0	2602	23,600	0
CH_2Ph	2400	13,000	+ 45	2632	28,000	+ 30
$CH_2 \cdot NH_2$	2410	10,500	+ 55	—	—	—
$CH_2 \cdot OH$	2410	12,000	+ 55	2638	24,500	+ 36
$CH_2 \cdot CN$	2424	10,500	+ 79	2657	23,000	+ 55
$CH_2 \cdot SH$	—	—	—	2672	27,000	+ 70
$CH_2 \cdot \overset{+}{N}H_3$	2455	11,500	+100	—	—	—
CH_2Cl	—	—	—	2712	23,000	+110
$CHCl_2$	—	—	—	2761	23,000	+159
CH_2Br	—	—	—	2767	23,500	+165
CH_2I	—	—	—	2910	23,500	+308
$CH:CH_2$	—	—	—	2867	26,500	+265
COMe	—	—	—	2980	28,000	+378
CHO	—	—	—	3047	28,000	+445

As already explained, 4-methoxy-4′-methyldiphenyl absorbs at only slightly longer wavelengths than 4-methoxydiphenyl (Δ, 7 Å). Electron-withdrawing α-substituents (B) cause much greater red-shifts. With substituents of low polarisability the displacement increases with the electron-withdrawing effect, as in the *p*-toluidine series, *e.g.*, in the order H < Ph < OH < CN. However, the phenyl substituent in 4-benzyl-4′-methoxydiphenyl is again responsible for a greater displacement of the *K*-band to longer wavelengths than could have been expected from its inductive effect alone, *i.e.*, from factor 1.

Similarly, the chloride (B = Cl) absorbs at longer wavelengths than the cyanide (B = CN), although the electron-withdrawing effect of CN is greater than that of Cl (cf. the dissociation constants of cyanoacetic acid and chloroacetic acid in Table 2). Most important, the red-shift of the *K*-band increases considerably from the chloride to the bromide and iodide, and from the alcohol to the thiol. The displacements increase as one ascends within a group in the Periodic Table, although the electron affinity decreases. The red-shifts due to factor 1 are obviously enhanced by another effect increasing in the opposite order. This is the polarisability of the C–B electrons (factor 2) which increases in the order CN < Cl < Br < I and OH < SH. It clearly demonstrates that these electrons participate in the electron migration of the transition.

This "polarisability" effect of the C–Hal electrons is much more important in this series than in the *p*-nitrotoluene series. Whereas 4-nitrobenzyl iodide absorbs at approximately the same wavelength as *p*-nitrotoluene, factors 1 and 2 cancelling each other, in 4-bromomethyl- and 4-iodomethyl-4′-methoxydiphenyl factor 2 makes much the greater contribution. The displacements of the *K*-band due to the increased polarity in in the ground state could be expected to be much smaller for the bromide and iodide than those found for the cyanide or chloride (55 and 110 Å respectively), but the observed displacements are 165 and 308 Å respectively. This shows that the polarisability of the CH_2–Hal electrons towards the C atom is smaller than that in the opposite direction. (A consideration of the different polarities of the CH_2–Hal bonds in the two series would only reinforce this conclusion).

In order to assess the contribution of the electronic polarisability of the C–Br and, in

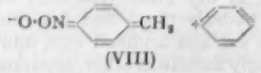
particular, of the C–I bond in its proper perspective, we have prepared and examined the spectra of 4-formyl-4′-methoxy-, 4-acetyl-4′-methoxy-, and 4-methoxy-4′-vinyldiphenyl (VI; CH_2B = CH:O, CMe:O, CH:CH_2). The maxima of the *K*-bands are compared in Table 3. They show that the displacement of the *K*-band due to the introduction of the CH_2I group into 4-methoxydiphenyl is appreciably greater than that produced by the CH:CH_2 group and almost as great as that caused by the COMe or CHO group, although in the latter cases the displacement is partly due to the increased polarity of the absorbing system. The effect of a C–I bond here is comparable to and even greater than that of a double bond.

Discussion.—Analysis shows that the effect of a terminal group on the position of *K*-bands depends on its polarisability and its influence on the polarity of the absorbing system, both factors varying the facility of the electron migration in the direction which determines the stability of the excited state. According to wave-mechanics, an electron passes on excitation into a new orbital divided by an (additional) nodal plane into two parts possessing wave-functions of opposite sign. In symmetrical systems such as atoms or the hydrogen molecule, the probability of finding the excited electron on either side of the nodal plane is equal, but in unsymmetrical systems the excited orbital can be expected to extend more to one side of the nodal plane. Our observations afford experimental evidence that the stability of the excited state is decided by the migration of the electron into the more stable part orbital of longer " life time," although the matter is slightly more complicated in the polyelectronic systems discussed in this paper.

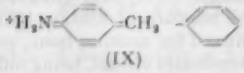
The observation that in substituted methyl groups the single bonds (A–C or C–B) partake in the electron migration within systems such as (VII) and that their polarisability may cause redshifts comparable to those due to multiple linkages such as C:C and C:O (VII; CH_2B = C:C, C:O) is of considerable theoretical significance, since it cannot be accounted for by the widely accepted theoretical interpretations of electronic spectra which are based on structures involving non-localised bonds and on the assumption that only the π-electrons of the absorbing systems are important or need to be considered for the electron transition.

(VII) $A{\cdot}CH_2{\cdot}[CH{:}CH]_n{\cdot}CH_2{\cdot}B$ ⟶

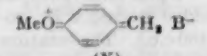
The observed effects are far too great to be attributed to some kind of hyperconjugation. Attempts to apply this conception to substituted methyl groups, in order to account for the considerable spectroscopic effects of single bonds, or at least for the contribution due to their polarisability, are also unsatisfactory, because they would make it necessary to assume that in the excited state and, to a smaller degree, in the ground state idealised structures such as (VIII) and (IX) would make an important contribution and that the contribution



(VIII)



(IX)



(X)

of structures (X) would increase in the order $Cl^- < Br^- < I^-$. This would be inconsistent with the known relative and absolute electron affinities and ionisation potentials of atoms (for the inadequacy of the conception of hyperconjugation, see also Burawoy and Spinner, *J.*, 1954, 3752; 1955, in the press; Sweeney and Schubert, *J. Amer. Chem. Soc.*, 1954, **76**, 4625).

One of us has already shown that the valency conception of non-localised bonds is in disagreement with numerous observations and is superfluous. The constitutive changes of covalent linkages and of their bond properties such as the bond energies, interatomic distances, dipole moments, as well as chemical changes, can be accounted for by the principles of the classical structural theories. They involve only inductive electron displacements and are caused by changes of the effective nuclear charges (the screening) of the participating atoms, *i.e.*, by changes of the repulsive interactions of electrons and nuclei which should also inhibit electronic delocalisation (Burawoy, *Trans. Faraday Soc.*, 1944, **40**, 537; *Discuss. Faraday Soc.*, 1951, **10**, 104; *Chem. and Ind.*, 1944, 434; " Contribution à l'Étude de la Structure Moléculaire," Liège, 1947—1948, p. 73; cf. also Lennard-Jones and Pople, *Discuss. Faraday Soc.*, 1951, **10**, 9).

The results of the present investigation afford additional support for this view. Thus, the electron migrations to the excited state in conjugated systems are not electromeric (as in XI), nor do they involve many-centred (non-localised) orbitals, but consist of inductomeric displacements of "localised" electrons (as in XII). According to this view a single bond should fulfil qualitatively and, if of sufficiently high electronic polarisability, quantitatively the same function as a double bond, as is, indeed, observed.

(XI) A-CH$_2$-CH=CH-CH=CH- A-CH$_2$-CH=CH-CH=CH- (XII)

On this basis, an absorbing conjugated system can be considered as a complex system of interacting smaller polarisable units (electron pairs or even the single electrons). An increase of the polarisability of any of these units either by an increase of the polarity of a bond or on replacement by other more strongly polarisable units will facilitate the electron migration and stabilise the excited state, *i.e.*, cause a red-shift of the *K*-band. In later parts of this series, these conclusions will be further supported by an analysis of the effect of other terminal groups on the position of *K*-bands and will be justified by a theoretical interpretation.

Experimental

Spectra were determined with a Hilger E3 quartz spectrograph fitted with a Spekker photometer, a tungsten-steel high-tension spark being employed as the source of light. If not otherwise stated, compounds investigated were obtained by known methods and purified. They had the physical characteristics previously reported, except that 4-aminobenzylamine obtained by Amsel and Hofmann (*Ber.*, 1886, **19**, 1285) as a liquid was found to be a highly hygroscopic solid, m. p. 37°, giving a urea derivative of m. p. 199—200° (Amsel and Hofmann give 197°).

p-*Nitrobenzotrichloride*.—Antimony pentachloride (3 c.c.) was added slowly to *p*-nitrobenzotribromide (5 g.) (Fisher, *J. Amer. Chem. Soc.*, 1934, **56**, 2470); the mixture was heated at 80° for 20 min., poured on ice and extracted with ether. After being washed with 10% aqueous sodium hydrogen carbonate and water and dried, the ether was removed and the residue of of p-*nitrobenzotrichloride* (0·7 g., 22%) recrystallised from light petroleum (b. p. 40—60°) forming needles, m. p. 47° (Found: C, 35·4; H, 2·1; N, 5·4; Cl 43·6. $C_7H_4O_2NCl_3$ requires C, 35·0; H, 1·7; N, 5·8; Cl, 44·2%).

4-p′-*Methoxyphenylbenzoyl Chloride*.—4′-Methoxydiphenyl-4-carboxylic acid (34·2 g.) (Fieser and Bradsher, *J. Amer. Chem. Soc.*, 1936, **58**, 1738, 2337) and thionyl chloride (250 g.) were refluxed gently for 2 hr. The excess of thionyl chloride was removed under reduced pressure and from the residue 4-p′-*methoxyphenylbenzoyl chloride* (27 g., 73%) was extracted with dry light petroleum (b. p. 60—80°). The same product was also obtained by the action of phosphorus pentachloride. It crystallised from light petroleum as plates, m. p. 100° (Found: Cl, 14·7. $C_{14}H_{11}O_2Cl$ requires Cl, 14·4%).

4-p-*Methoxyphenylbenzyl Alcohol*.—The acid chloride (25 g.) in dry ether (750 c.c.) was added during 2 hr. to a stirred mixture of lithium aluminium hydride (3 g.) and dry ether (400 c.c.). The mixture was refluxed for another hour, poured on ice, and acidified with dilute sulphuric acid. 4-p-*Methoxyphenylbenzyl alcohol*, being only sparingly soluble in ether, separated (16 g., 74·5%). Alternate recrystallisation from ethanol and light petroleum (b. p. 60—80°) gave plates, m. p. 164° [Found: C, 78·6; H, 6·2%; *M* (Rast), 214. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%; *M*, 214·2]. This compound can also be prepared on a small scale by direct reduction of 4-*p*-methoxyphenylbenzoic acid.

4-p-*Methoxyphenylbenzyl Chloride*.—A solution of the alcohol (4·5 g.) and thionyl chloride (3·5 g.) in chloroform (70 c.c.) was heated at 40° for 1 hr. and refluxed for 15 min. After cooling, it was washed with water, aqueous sodium hydrogen carbonate, and again with water, dried (Na_2SO_4), and evaporated. The residue was extracted with hot light petroleum (b. p. 60—80°) from which the *chloride* separated on cooling (4·0 g., 92%). It crystallised from light petroleum as plates (or clusters of needles), m. p. 103·5—104° (Found: C, 72·0; H, 5·6; Cl, 15·0. $C_{14}H_{13}OCl$ requires C, 72·3; H, 5·6; Cl, 15·2%).

4-p-*Methoxyphenylbenzyl Bromide*.—A solution of the alcohol (1 g.) and phosphorus pentabromide (3·5 g.) in chloroform (25 c.c.) was heated at 40° for 30 min. and then raised to the b. p. This gave the *bromide* (0·8 g., 62%), plates (from light petroleum), m. p. 114° (Found: C, 60·6; H, 4·7; Br, 28·8. $C_{14}H_{13}OBr$ requires C, 60·65; H, 4·7; Br, 28·8%).

4-p-*Methoxyphenylbenzyl Iodide*.—The chloride (1·0 g.) in acetone (10 c.c.) was mixed with potassium iodide (1·0 g.) in water (6 c.c.) and acetone (60 c.c.), set aside in the dark for 4 hr.,

and then boiled for 5 min. After cooling, it was poured into water (1 l.), a solution of sodium thiosulphate (3 g.) added, and the precipitate of *iodide* filtered off without delay (1·0 g., 70%). Recrystallisation in semidarkness from light petroleum (b. p. 60—80°) gave light-sensitive pale yellow needles, m. p. 114° to 122° (decomp.), depending on the rate of heating (Found: C, 52·4; H, 4·3; I, 38·8. $C_{14}H_{13}OI$ requires C, 51·9; H, 4·0; I, 39·15%).

4-p-*Methoxyphenylbenzyl Cyanide*.—A solution of the chloride (0·6 g.) and sodium cyanide (1·2 g.) in acetone (15 c.c.) and water (10 c.c.) was refluxed for 3 hr. After filtration, water was added and the precipitated *cyanide* was collected (0·3 g., 50%). Alternate crystallisation from light petroleum and ethanol gave plates, m. p. 128—129° (Found: C, 80·2; H, 5·9. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·9%).

4-p-*Methoxyphenyltoluene-ω-thiol*.—A solution of sodium sulphide nonahydrate (1 g.) in water (3 c.c.) and ethanol (15 c.c.) was saturated with hydrogen sulphide. 4-*p*-Methoxyphenylbenzyl chloride (1 g.) in ethanol (30 c.c.) was added and the mixture refluxed for 10 min. After cooling and addition of water (100 c.c.), the precipitate was filtered off, washed with water, and extracted with a solution of sodium hydroxide (1 g.) in ethanol (50 c.c.) and water (110 c.c.). The solution was acidified quickly by the addition of concentrated hydrochloric acid (10 c.c.), and the precipitated *thiol* (0·4 g., 40%) collected and washed with water. Crystallisation from ethanol or light petroleum gave white plates, m. p. 103—104° (Found: C, 72·4; H, 6·4. $C_{14}H_{14}OS$ requires C, 73·0; H, 6·1%).

4-*Benzyl-4′-methoxydiphenyl*.—To a boiling solution of 4-*p*-methoxyphenylbenzophenone (8 g.) (Fieser and Bradsher, *loc. cit.*) in absolute ethanol (1 l.), sodium (40 g.) was added during 30 min. After cooling, carbon dioxide was passed into the solution until a sample diluted with water was not alkaline to phenolphthalein. The sodium hydrogen carbonate was filtered off and the filtrate concentrated to 80 c.c. On cooling, 4-*benzyl-4′-methoxydiphenyl* separated (5·5 g., 70%). It crystallised from methanol as plates, m. p. 100—100·5° (Found: C, 87·2; H, 6·8. $C_{20}H_{18}O$ requires C, 87·6; H, 6·6%).

4-p-*Methoxyphenylbenzaldehyde*.—Chromium trioxide (5·2 g.) was dissolved in *tert.*-butyl alcohol (14 g.), benzene (35 c.c.) was added, and the water removed with anhydrous sodium sulphate. The solution of *tert.*-butyl chromate was added to 4-*p*-methoxyphenylbenzyl alcohol (10 g.) in benzene (500 c.c.) at 45°, the mixture being kept at this temperature for another hour and at room temperature for 24 hr. A solution of hydrazine sulphate (5·2 g.) in 10% sulphuric acid (400 c.c.) was added and the mixture stirred for 1 hr. The benzene layer was separated, washed, dried ($MgSO_4$), and evaporated. The residual *aldehyde* (8·1 g., 82%) was obtained after alternate crystallisation from light petroleum and ethanol as needles, m. p. 104—105° (Found: C, 79·1; H, 5·6. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%).

4-p-*Methoxyphenylbenzylidene Dichloride*.—To a solution of the benzaldehyde (2 g.) in chloroform (12 c.c.) phosphorus pentachloride (6 g.) was added and the mixture refluxed for 15 min. After cooling, it was shaken with ice-water, aqueous sodium hydrogen carbonate, and water. After drying ($MgSO_4$), the chloroform was removed and the residual *dichloride* (1·3 g., 52%) crystallised from light petroleum (b. p. 40—60°) as plates, m. p. 113—114° (Found: C, 63·1; H, 4·5; Cl, 26·2. $C_{14}H_{12}OCl_2$ requires C, 62·9; H, 4·5; Cl, 26·5%). Attempts to prepare the dibromide were unsuccessful.

4-(1-*Hydroxyethyl*)-4′-*methoxydiphenyl*.—A hot solution of 4-*p*-methoxyphenylacetophenone (Fieser and Bradsher, *loc. cit.*) (5·0 g.) in benzene (100 c.c.) was added slowly to lithium aluminium hydride (1·5 g.) in dry ether (125 c.c.). After 6 hours' refluxing, ice and dilute sulphuric acid were added, and the organic layer was separated, washed with 10% aqueous sodium hydroxide, and water, dried ($MgSO_4$), and concentrated to 10 c.c. On cooling, the *alcohol* (4 g., 80%) separated. Crystallisation from light petroleum (b. p. 60—80°) gave needles, m. p. 121—122° (Found: C, 79·1; H, 6·9. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%).

4-p-*Methoxyphenylstyrene*.—The preceding alcohol (3·0 g.) and phosphorus pentabromide (8·0 g.) in chloroform (125 c.c.) were heated at 40° for 1 hr. and subsequently boiled for a few minutes. After being washed with water and 10% aqueous sodium hydrogen carbonate the chloroform solution was dried ($MgSO_4$) and the solvent was removed. The residual bromide (3·3 g., 85%) was crystallised once from light petroleum or carbon tetrachloride. The slightly impure bromide (1·5 g.) was refluxed for 20 min. with a solution of calcium formate (0·4 g.) in 90% formic acid (50 c.c.). On addition of water (25 c.c.) and cooling, 4-p-*methoxyphenylstyrene* separated almost quantitatively. Crystallised from carbon tetrachloride or benzene it had m. p. 173—174° (Found: C, 85·7; H, 6·6. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%).

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The Kinetics and Mechanism of the Polymerization of Ethyleneimine.

By W. G. Barb.

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The polymerization of ethyleneimine catalyzed by water and by various organic acids has been investigated by dilatometric kinetic measurements and by paper-chromatographic examination of the products. Pure, dry ethyleneimine reacts very slowly, even at high temperatures; traces of water greatly increase the rate. Acid catalysts produce much greater rates even at lower temperatures; water is not essential as a co-catalyst for these. The results are interpreted in terms of a stepwise reaction of iminium ions with uncharged imine-rings. Though the reaction is an addition polymerization, and there are, at any instant, only a small number of reactive iminium ions present, the overall characteristics are similar to those of a typical stepwise poly-condensation because of a very rapid "transfer equilibrium" of hydrogen ions between the various entities present.

The kinetics of reaction for various acids have been examined. The fractional consumption of catalyst during the reaction is as great as, or greater than, the fractional consumption of monomer; the kinetics of monomer conversion are therefore largely determined by the kinetics of catalyst destruction and hence vary from one catalyst to another. With weak acids it is assumed that ion-pairs, rather than free iminium ions and cations, are present.

Of the many polymerizations known only two, vinyl polymerization and polycondensation, have until recently been extensively investigated physicochemically to elucidate details of the reaction mechanism. Recently a third type, the formation of polypeptides from *N*-carboxy-anhydrides, has begun to be similarly investigated. Amongst polymerizations of which little is known regarding exact details of mechanism (though much empirical information may be available) is the addition polymerization of the three-membered ring compound, ethyleneimine. The earlier investigations of Kern and Brenneisen (*J. prakt. Chem.*, 1941, **159**, 193, 219) and of Jones and his co-workers (Jones, Langsjoen, Neumann, and Zomlefer, *J. Org. Chem.*, 1944, **9**, 125; Jones, *ibid.*, p. 484) had established certain facts bearing on the mechanism, and these are summarized below.

Amongst the findings of Kern and Brenneisen are the following: (i) Acids catalyze the polymerization. In particular, 40% aqueous hydrogen bromide and borofluoroacetic, toluene-*p*-sulphonic, and sulphanilic acid were employed. (ii) Various bases known to catalyze the polymerization of ethylene oxide proved ineffective for the polymerization of ethyleneimine. (iii) Peroxides, used under similar conditions to those employed for the acid catalysts, did not cause polymerization, but since the conditions involved temperatures of 40° or 50°, at which the peroxides would not decompose appreciably, these experiments are inconclusive. (iv) Inhibitors of free-radical vinyl polymerizations do not inhibit ethyleneimine polymerization. (v) The reaction frequently proceeds explosively, particularly if a certain catalyst concentration or a certain temperature is exceeded. (vi) The reaction catalyzed by sulphanilic acid seems to be intermediate between a first- and a second-order reaction in ethyleneimine. (vii) Acetylation of the polymer yielded a 1 : 1 acetyl derivative, but benzoylation gave derivatives apparently containing more nitrogen than corresponded to a 1 : 1 compound.

Jones and his co-workers found, amongst other results, that: (i) Ethyleneimine in the absence of catalysts is very stable, even at 150°. (ii) Substances which catalyze polymerization are those capable of producing quaternary iminium nitrogen, *i.e.*, acids, alkylating agents, etc. (iii) The (refractometrically measured) kinetics of polymerization of ethyleneimine in dilute hydrochloric acid are complicated. The reaction is of a very high order in ethyleneimine, though the quarter-life is inversely proportional to the initial ethyleneimine

concentration; the half-life was inversely proportional to the initial acid concentration. (iv) Benzoylation of poly(ethyleneimine) gave a substance whose nitrogen content corresponded approximately to that of a 1 : 1 compound.

(I)

It seem therefore that the reaction proceeds *via* iminium intermediates [*e.g.* (I)], but the course of the reaction is not clear and there is uncertainty as to whether the polymer is linear or branched.

Experimental

Materials.—The procedures used for preparing ethyleneimines followed these workers: Ethyleneimine, Wenker (*J. Amer. Chem. Soc.*, 1935, **57**, 2328). *N*-(*n*-Butyl)ethyleneimine, Elderfield and Hageman (*J. Org. Chem.*, 1949, **14**, 605). *N*-(2-Aminoethyl)ethyleneimine ("ethyleneimine dimer") from 2-amino-2′-hydroxydiethylamine (Jones *et al.*, *loc. cit.*).

n-Butylamine and piperidine were fractionally distilled before use. The acid catalysts used were recrystallized commercial samples. "AnalaR" phenol was used without further purification.

Density and Thermal Expansion of Ethyleneimine and Volume Change on mixing with Water.—These quantities were required for the analysis of dilatometric kinetic measurements. Density was measured by distilling sodium-dried ethyleneimine *in vacuo* into dilatometers (1-mm. bore "Veridia" stems; bulb capacity approx. 0·5 ml.) calibrated with absolute alcohol. d_4^{25} was 0·831 ± 0·001, and over the range 25—65° the volume coefficient of expansion was $1·3 \times 10^{-3}$ (volume per unit volume at 25° c per °c). By extrapolation d_4^{100} should be 0·756 (Found, by immersing a dilatometer in a steam-bath, 0·752) (Gabriel and Stelzner, *Ber.*, 1895, **28**, 2929, give the s. g. at 24° as 0·8321, corresponding to d_4^{25} 0·831, and Jones *et al.*, *loc. cit.*, give d_{25}^{25} 0·835, corresponding to d_4^{25} 0·832, both in agreement with the present value).

The volume contraction on mixing ethyleneimine and water was measured in a small pycnometric flask and in dilatometers. Five measurements for mixtures ranging from 10% to 70% (by wt.) of water gave a value of 23 ± 4% for the change in volume per volume of water used in forming a 1 : 1 hydrate (*i.e.*, where the molar concentration of water was greater than that of ethyleneimine, the volume change was calculated as a percentage of the volume of water equivalent to the ethyleneimine used). This volume change is much less than those for water plus methylamine or ethylamine, which (calculated from data in Beilstein's "Handbuch") are of the order of 40—60%. Similar experiments on mixtures of ethyleneimine and ethanolamine showed that any volume change occurring was within the limits of experimental error.

pK_b of Ethyleneimine and of N-(n-Butyl)ethyleneimine.—Certain features of the polymerization suggested that ethyleneimine was an abnormally weak base compared with aliphatic amines. This was tested by pH titration of approximately 0·01N-ethyleneimine solution with 2N-hydrochloric acid at 25°, with the arrangement described by Waley and Watson (*Biochem. J.*, 1953, **55**, 328). The total titre was within 1% of the theoretical value, and the titration curve was perfectly reproducible.

The basic dissociation constant K_b is defined as $K_b = (BH^+)(OH^-)/(B)$, the terms in parentheses representing activities; if the Debye–Hückel relation for activity coefficients is applied, then

$$pK_b = pK_w - pH - \log[BH^+]/[B] + 0·5\sqrt{\mu} - C'\mu,$$

where C' is a constant and μ the ionic strength (cf. Glasstone, "The Electrochemistry of Solutions," Methuen, London, 1937, Chap. IX). From the complete titration curve, pK_b was calculated at values of $[BH^+]/[B]$ from 0·1 to 5, neglecting $C'\mu$; pK_b so obtained ranged from 6·045 to 6·155, corresponding to $K_b = 7 \times 10^{-7}$ to 9×10^{-7}. K_b for ethyleneimine is thus some 100 times less than for most aliphatic amines. Similar measurements on *N*-(*n*-butyl)ethyleneimine gave $K_b = 6·5 \times 10^{-7}$ to 8×10^{-7}.

It seems likely that the abnormally low basicity of ethyleneimine and the instability of the three-membered ring under the influence of acids are related phenomena. The abnormal value to which the C–N–C bond-angle in ethyleneimine is constrained presumably affects the electronic structure and hence the availability of the nitrogen lone-pair electrons for dative-bond formation; correspondingly, if such a bond is formed by addition of a proton, the stability of the ring is impaired.

Estimation of Percentage Conversion of the Reaction Mixture.—Kern and Brenneisen (*loc. cit.*) estimated the residual ethyleneimine by chilling to stop the reaction and distilling the ethyleneimine *in vacuo* into standard acid; the back-titration of the excess of acid and a direct weighing

of the polymer residue gave concordant results, but in the writer's experience this method is unsatisfactory because it is difficult to know where to stop the distillation; in a high vacuum some material distils readily but the distillation can be continued to give further material which is not ethyleneimine (being comparatively non-volatile and odourless) and must consist of low polymers. Further, it is well known from other polymer systems that the complete removal of monomer from polymer by mere distillation is very difficult, so that the employment of a low vacuum, in which only ethyleneimine distils readily, would not solve the problem.

Jones *et al.* (*loc. cit.*) estimated conversions viscometrically and refractometrically. In each case the method was calibrated with solutions of poly(ethyleneimine), and possible changes in degree of polymerization (DP) with extent of reaction were neglected. In fact these changes are of the greatest importance, as will be shown later, and the viscometric method is therefore valueless. The extent to which the refractometric method applies cannot be stated in view of the lack of data on polymers of different degrees of polymerization, but it is likely to be reasonably sound.

In the present work reaction rates were followed dilatometrically. The dilatometers (below) were repeatedly washed with hot alcohol before use, attached to a high-vacuum line by standard ground joints, thoroughly pumped out, and weighed. Acid catalysts were introduced as solutions in a volatile solvent (chloroform, ether, or acetone) and the solvent was pumped off. Other materials (ethyleneimine, added amines, etc.) were distilled into the dilatometers *in vacuo*; known weights of water, *n*-butylamine, ethyleneimine dimer, etc. were taken from graduated capillary reservoirs. The dilatometers were sealed off and weighed (after completion of the kinetic measurements) together with the ground-joint " stump," thus obtaining the total weight of the contents. The weight of ethyleneimine was deduced by difference.

Readings at 40° were obtained by observing the meniscus with a cathetometer. From observations on very slow reactions it was concluded that the initial temperature equilibration in the thermostat was very rapid (*ca.* 1 min.) and the level of the meniscus at zero time could be obtained by extrapolation. For experiments at 100° the dilatometers were mounted in a glass " steam-tower " and continuous readings were taken; temperature equilibration was slower (*ca.* 10 min.) but since the rates were all very slow extrapolation to zero time was again easy. At higher temperatures a " vapour-tower," with different refluxing liquids, could be used, were it not for a tendency of an appreciable fraction of the dilatometers to explode. Therefore an initial reading of the meniscus-to-top distance on the dilatometer was taken in a bath at 25°, the dilatometer was then placed in a brass screw-cap tube and immersed in an oil-bath at 130° or 160° for a certain time, withdrawn, chilled, and returned to the bath at 25°; at least 6 hr. were then allowed for capillary drainage before the next reading. Serious errors arise without such drainage, particularly if the mixture is fairly viscous. (The reaction rate at 25° was shown to be negligible in these experiments).

For all runs in the presence of added substances, the volume change was calculated as a percentage of the initial volume of ethyleneimine only (not of the total volume).

Calibration of Dilatometric Method.—A Kjeldahl-type distillation was used. After a known volume contraction had occurred, the contents of the dilatometer were frozen into the bulb, which was cut off and dropped into approx. 40 ml. of *ca.* 0·1N-alkali. About 30 ml. of this solution were distilled into cold standard hydrochloric acid and the excess of acid was back-titrated (methyl-orange). Distillation of a further 5 ml. of the remaining solution gave no further basic material, so that the method has an advantage over " dry " distillation (see above). It is essential to distil from an alkaline solution, otherwise polymerization occurs during the distillation. As a check, known amounts of ethyleneimine were sealed in ampoules which were then broken under the solution to be distilled :

Contents of ampoule (mg.)	282	823	250	215
Solution from which distilled	H_2O	H_2O	0·1N-NaOH	0·1N-NaOH
Titre equiv. of distillate (mg.)	241	714	252	213
Recovery (%)	86	87	101	99

The end-point of the titration of ethyleneimine with dilute acid is quite stable at room temperature, but, on boiling, the solution becomes alkaline owing to the formation of 2-chloroethylamine (Gabriel, *Ber.*, 1888, **21**, 1049).

Steam-distillations were carried out on a number of mixtures which had reacted under various conditions. The results are summarized in the Table. Though there is some experimental scatter it will be seen that the conversion factor F increases a little as the conversion increases; this was at first believed to be an artefact due to incomplete capillary

drainage of the more viscous, highly polymerized solutions, but careful attention to this failed to eliminate the trend. Subsequently an elucidation of the reaction mechanism provided a ready interpretation.

TABLE. *Volume contraction on polymerization of ethyleneimine.*

Water or catalyst added (%) *	Conversion (%)	p	Contraction (%) Expt.	Calc.	F †	$F_{calc.}$ ‡
(a) Reaction at 160°, volumes measured at 25°. No added catalyst.						
—	31·8	0·174	3·87	3·48	12·15	10·95
—	41·8	0·235	4·98	4·70	11·9	11·25
—	69·1	0·433	8·66	8·66	12·55	12·55
—	72·3	0·474	9·23	9·48	12·75	13·1
—	72·5	0·475	9·70	9·50	13·35	13·1
—	79·0	0·542	10·18	10·84	12·9	13·75
(b) Reaction at 130°, volumes measured at 25°. Water added.						
0	28·6	0·154	3·30	3·08	11·5	10·8
0·5	51·2	0·300	6·02	6·00	11·75	11·7
3·0	54·1	0·322	6·53	6·44	12·1	11·9
0	56·3	0·338	7·15	6·76	12·7	12·0
0	59·5	0·363	7·20	7·26	12·1	12·2
5·0	70·1	0·452	9·65	9·04	13·75	12·9
2·0	71·7	0·467	9·75	9·34	13·6	13·05
0	73·4	0·484	10·30	9·68	14·0	13·2
0	74·3	0·494	10·31	9·88	13·9	13·3
0	75·0	0·500	10·42	10·00	13·9	13·35
1·0	80·5	0·558	11·28	11·16	14·0	13·85
2·0	86·2	0·602	12·2	12·04	14·2	14·05
(c) Reaction at 40°, volumes measured at 40°. Catalyst added.						
3·60, BZ	36·3	0·202	4·02	4·04	11·1	11·15
0·85, CA	63·6	0·397	8·19	7·94	12·9	12·45
2·25, TS	70·6	0·458	8·92	9·16	12·65	13·0
0·75, TS	73·7	0·487	9·75	9·74	13·25	13·25
2·50, CA	77·8	0·529	10·80	10·58	13·9	13·6
3·80, TS	83·8	0·597	12·30	11·94	14·7	14·25
7·85, CA	91·8	0·714	13·35	14·28	14·55	15·5
(d) Reaction at 100°, volumes measured at 100°. Water added.						
12	53·0	0·314	8·1	7·85	15·3	14·8
3	59·4	0·362	9·55	9·05	16·1	15·2
22	80·4	0·557	14·4	13·9	17·9	17·3
23	81·5	0·569	13·2	14·2	16·2	17·45

* BZ = benzoic acid, CA = chloroacetic acid, TS = toluene-*p*-sulphonic acid.
† F = conversion factor = percentage volume contraction for 100% conversion of monomer to polymers.
‡ $F_{calc.}$ = calculated conversion factor.

Interpretation of Dilatometric Data.—Since the polymerization of ethyleneimine is essentially stepwise the main product in the early stages is ethyleneimine dimer, and the mean degree of polymerization of the polymer increases throughout the reaction. The density of the dimer is given by Jones *et al.* (*loc. cit.*) as d_{25}^{25} 0·92, so the volume contraction for conversion into the dimer is 9·3% to which figure the conversion factor should extrapolate at very low conversions. At higher conversions the volume contraction due to consumption of monomer will have superimposed on it contractions due to the reaction of polymer molecules with one another. To examine this point further, we shall assume that (i) the molecular weight distribution is similar to that calculated by Flory for polycondensations (*J. Amer. Chem. Soc.*, 1936, **58**, 1877; 1939, **61**, 3339) and is independent of the rate of reaction, temperature, etc. (the reasons for these assumptions will be discussed in connection with the reaction mechanism), and (ii) the volume contraction accompanying the opening of an ethyleneimine ring is independent of the attached structure, *e.g.*, the reaction of trimer with dimer produces the same volume change as two monomer molecules' reacting.

According to Flory's equations, if p is the fraction of functional units (imine rings in this case) which have reacted (*i.e.*, opened to linear structures), then the fraction x of monomer remaining is

$$x = (1 - p)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

From the percentage conversion, $100\ [1 - (1 - p)^2]$, p is known. The percentage volume contraction can then be calculated, by assuming it to be proportional to p and taking the value of 9·3% contraction at 25° for $p = 0{\cdot}5$, derived from the densities of monomer and dimer.* In fact it was found that if a value of 10·0% contraction for $p = 0{\cdot}5$ was adopted instead (corresponding to a dimer density of 0·925), the calculated conversion factors agreed with the values experimentally determined at 25° within the estimated limits of the total experimental error (cf. Table).

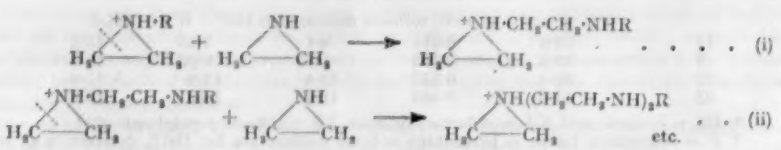
Results at 40°, of experiments with various acid catalysts, can be very well fitted in the same way as those at 25°, by taking 10% contraction for $p = 0{\cdot}5$. A smaller number of measurements at 100° are also shown in the Table; these are more erratic, but can be reasonably interpreted in terms of a volume change of 12·5% at 100° for the conversion of monomer into dimer.

Chromatographic Technique.—Paper chromatograms were run downwards on Whatman No. 1 filter paper using butanol–acetic acid–water–pyridine (9 : 2 : 4 : 6). The spots were developed with ninhydrin, or with cobalt chloride–ninhydrin (Wiggins and Williams, *Nature*, 1952, **170**, 279). With these reagents the various ethyleneimine polymers give purplish-mauve and salmon-coloured spots, respectively, with the exception of the dimer which gives a more yellowish-brown spot. The colours are presumably due to terminal $\cdot NH_2$ groups, not to $\cdot NH\cdot$ groups in the chain, since the ninhydrin-blue colour is developed with primary but not with secondary amines. Ethyleneimine itself gives no colour with ninhydrin, and piperazine [alleged by Jones *et al.* (*loc. cit.*) to be formed as a polymerization by-product] gives a very faint brownish spot. Amino-alcohols give deep reddish-purple spots.

The dimer spot was identified by running a marker of the synthesized material, and the spots of successively lower R_F were taken to be trimer, tetramer, etc. A fresh chromatogram may reveal up to seven discernible spots or bands (*i.e.*, up to the octamer), with an unresolved "streak" of higher polymer. In addition, two very faint spots are sometimes found of higher R_F than the dimer spot; these were shown by markers to be caused by minute traces of ethanolamine and 2-amino-2′-hydroxydiethylamine (the hydrolysis product of the dimer), respectively.

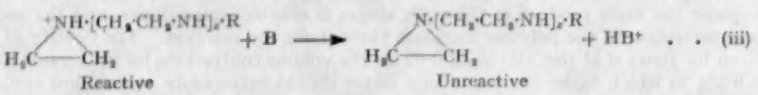
Discussion

Mechanism and Chromatographic Examination of the Reaction.—Jones *et al.* (*loc. cit.*) suggested that the polymerization of ethyleneimine proceeded *via* ionic intermediates, thus :



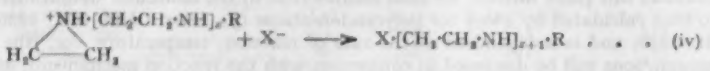
(i) (ii)

In order to account for the catalysis by, for example, benzyl halides, it was assumed that R need not be H but could also be an organic radical. Termination (*i.e.*, deactivation of the reactive iminium ions) could occur either by proton abstraction :



(iii)

(where B is any base, such as a monomer molecule, amino- or imino-nitrogen in a polymer, an anion, water, etc.) or by ring opening with an anion :

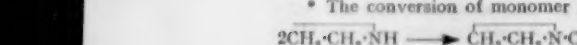


(iv)

In reaction (iv), the place of X^- could, hypothetically, be taken by amino-nitrogen in a polymer molecule, the product then being a branched polymer-ion.

Two important implications of such a reaction scheme were overlooked by Jones *et al.* (*loc. cit.*). First, reaction (iii) should obviously be written as an equilibrium. The actual

* The conversion of monomer into dimer corresponds to half the initial rings being opened, thus



polymer-growth is relatively slow and protons will always be distributed amongst the various basic centres in the polymerizing mixture. If it is assumed that the basicities of the imino-nitrogen in the monomer and in the polymer molecule are similar, it follows that in the early stages of reaction most of the protons will be attached to monomer molecules and therefore most of the product will be dimer. Only as the dimer concentration becomes significant compared with the monomer concentration will appreciable quantities of trimer, tetramer, and higher polymers be formed. The mean degree of polymerization will rise throughout the reaction and towards the end all lower species such as monomer, dimer, and trimer will disappear. This has been confirmed from a series of chromatograms of the products of a reaction of ethyleneimine containing 3·6% of chloroacetic acid at 40°. Two drops of the reaction mixture were withdrawn at various times and dissolved in 0·1N-sodium hydroxide to stop the reaction; these samples were chromatographed. The approximate conversion was estimated by dilatometric measurements on an identical reaction mixture.

By analogy with the transfer reaction in vinyl polymerization (Flory, *J. Amer. Chem. Soc.*, 1937, **59**, 241), we may speak here of "transfer equilibrium." Its consequence is that while there are only a limited number of reactive centres, as in a vinyl polymerization, yet the degree of polymerization rises throughout the reaction, as in a polycondensation where all molecules have reactive groups. Further, the distribution of protons amongst the various species will only be a function of their relative concentrations and basic strengths; the molecular-weight distribution at a given conversion will be independent of the catalyst used or of its concentration, as is found experimentally. It is, of course, conceivable that similar transfer equilibria would operate in other types of ionic polymerizations, such as cationic vinyl polymerizations (cf. Pepper, *Quart. Rev.*, 1954, **8**, 88), but experimental evidence is lacking.

The second aspect not discussed by Jones *et al.* (*loc. cit.*) is the addition reaction of two poly(ethyleneimine) molecules. There is no reason why such a reaction should not occur, since it is no different in kind from the polymerization of other *N*-substituted ethyleneimines. Chromatograms show that this reaction of polymers with one another undoubtedly occurs, since prolonged reaction causes all low polymer species to disappear, though there would be insufficient monomer left for them to be converted into high polymers by addition of monomer only; furthermore, the self-polymerization of the synthesized "ethyleneimine-dimer" has been demonstrated by Jones *et al.* (*loc. cit.*). Some aspects of this matter, which bear on the general polymerization mechanism of *N*-substituted ethyleneimines, will be discussed in the following paper.

We shall consider a reaction mixture for which the following are assumed: (*a*) All ethyleneimine rings (whether monomeric or at the end of a polymer chain) are of equal reactivity. (*b*) All nitrogen atoms (*i.e.*, amino- and imino-centres) are of equal basicity; with this assumption the percentage of any particular basic species B present as BH^+ remains constant throughout a polymerization for a given total acid concentration, and the kinetic treatment is thereby greatly facilitated. (*c*) There is an instantaneous transfer equilibrium (as previously described) so that all imine rings can be regarded as having the same functionality, even though at any instant only a part of them will have protons attached.

On this basis the formal treatment of molecular-weight distribution becomes identical with Flory's (*locc. cit.*) (cf. p. 2567). In addition we shall also assume (*d*) that the catalyst concentration does not change significantly during the reaction. The formal treatment of polymerization *rates* then becomes very simple. The aspect of particular interest here is that the reaction is of the second order in "imine-rings" [cf. reaction (ii) and assumption (*b*)], and therefore

$$1/(1-p) - 1 = p/(1-p) = kt \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

By substitution from (1)

$$x^{-0.5} - 1 = kt \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

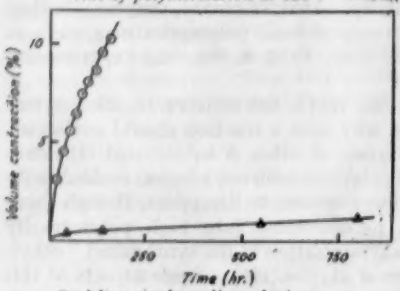
The form of this equation is that for a reaction of order 1·5 with respect to monomer. [Though the molecular-weight distribution functions which obtain here are the same as

those developed by Flory (*locc. cit.*), the rate equations are not the same because of the chemical differences between the two systems.] Our kinetic results will be examined in relation to the scheme just discussed, to decide what modifications (if any) of the original assumptions must be made.

Kinetic Results

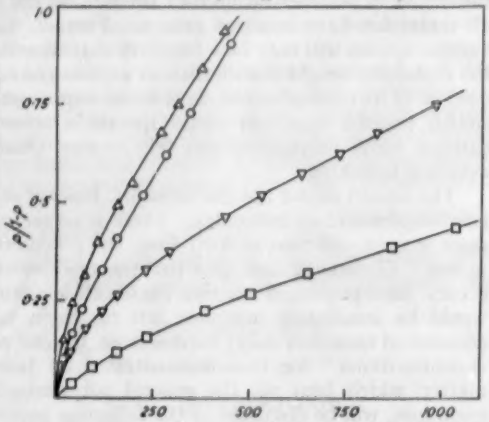
The Catalytic Action of Water.—Preparation of dry ethyleneimine. The ethyleneimine used in the early stages of this work was kept over freshly-cut sodium in a flask attached to the vacuum line, and was distilled *in vacuo* into a storage vessel next day. A certain irreproducibility in the results so obtained was attributed to varying amounts of water, and the ethyleneimine was subjected to additional drying. After standing over sodium for several days, the dry ethyleneimine was distilled *in vacuo* on to fresh sodium which had been heated *in vacuo*. If cooled by solid carbon dioxide the sodium slowly dissolved to give a deep blue solution; this colour must be related to that of solutions of sodium in liquid ammonia and of other alkali metals in certain simple aliphatic amines (cf. Moissan, *Compt. rend.*, **1899**, **128**, 26; Rengade, *ibid.*, **1905**, **140**, 246; **141**, 196). On warming, the blue colour faded and hydrogen was evolved, the final product being, presumably, *N*-sodio-ethyleneimine; a yellowish-white

Fig. 1. *Effect of drying of ethyleneimine on rate of polymerization at 130°.*



○ After single sodium-drying.
△ After special drying procedure.

Fig. 2. *Reaction course for different acid catalysts at 40°.*



Concentrations in moles/1000 g. of mixture. △, 0·625M-chloroacetic acid; ○, 0·54M-toluene-*p*-sulphonic acid; △, 1·00M-benzoic acid; □, 0·88M-dichlorophenol.

powder is deposited if appreciable quantities of sodium are allowed to react. The ethyleneimine was allowed to dissolve sodium till some of the derivative was precipitated, and was then distilled *in vacuo* into another flask which had been carefully pumped out. It is significant that no blue colour with sodium was formed, even in the cold, if the ethyleneimine had not been subjected to the preliminary sodium-drying; the blue colour is evidently very readily destroyed by traces of water.

Kinetic measurements. Fig. 1 shows the course of reaction at 130° for ethyleneimine subjected to one sodium-drying only and for ethyleneimine treated by the special drying procedure. The removal of the last traces of water very greatly reduces the reaction rate, and it is likely, particularly in view of the reaction mechanism developed later, that perfectly dry ethyleneimine would not polymerize at these temperatures.

The curve for partially dried ethyleneimine in Fig. 1 is similar to those obtained with the specially dried ethyleneimine to which known small amounts of water (<5% by weight) had been added. A general feature of all these curves is that the initial reaction rate declines rapidly *before* a significant fraction of the ethyleneimine has been consumed. This is best shown by assuming that the reaction is of some particular order with respect to ethyleneimine monomer (x) or unopened rings ($1 - p$), and plotting the corresponding kinetic function which should be linear with time. The graphs are roughly linear for values of p above about 0·13,

i.e., for monomer conversions greater than about 25%; below that value, the reaction rate is relatively much too fast and declines rapidly with increasing conversion. If the reaction is supposed to be of higher order, say second order in monomer, then the corresponding plot $[(1-p)^{-2}-1]$ against t is again approximately linear, this time down to conversions of approximately 20%, but below that there is still a marked fast phase. (As will be shown, other acid catalysts show a similar phenomenon.)

The possibility that the volume change observed in the fast phase of the reaction might be attributable to an initial conversion of water into ethanolamine, $\overline{CH_2\cdot CH_2\cdot NH} + H_2O \longrightarrow HO\cdot CH_2\cdot CH_2\cdot NH_2$, was considered. The volume change for this reaction calculated from the densities and volume changes on mixing is 28% of the volume of water reacting. This was found to bear no relation to the volume contraction in the initial fast phase, which seems practically independent of the water concentration. Further, chromatograms show that ethanolamine is formed only in minute traces.

Though the shape of the reaction curve is reproducible, the actual reaction rates varied by up to a factor of two, probably because during the long reaction times at the high temperatures involved traces of materials affecting the hydrogen-ion concentration are leached out of the glass; as will be shown, the reaction is catalyzed by hydrogen ions. Unsuccessful attempts were made to use silica dilatometers. These could be burnt out before use, but it appeared that ethyleneimine was afterwards very firmly adsorbed on the silica surface because charring always occurred on sealing off the dilatometers, even though the bulb was cooled in liquid air. The only generalizations possible are that the rate increases somewhat with increasing water concentration, and that rates at 100° are some 2—3 times less than those for corresponding mixtures at 130°. At 40° ethyleneimine containing 1% of water did not react detectably during several weeks.

Reactions in the presence of added acid catalysts proved reproducible and detailed kinetic conclusions could be drawn.

The Reaction catalyzed by Added Acids.—The rate of polymerization of ethyleneimine in the presence of various acids was examined to ascertain the nature of the conversion–time curve, the dependence of rate on acid concentration, and the relative catalytic efficiency of the various acids. Five catalysts, toluene-*p*-sulphonic acid (2×10^{-1}), monochloroacetic acid ($1{\cdot}5 \times 10^{-3}$), benzoic acid ($6{\cdot}5 \times 10^{-5}$), 2 : 4-dichlorophenol ($3{\cdot}1 \times 10^{-8}$), and phenol ($1{\cdot}3 \times 10^{-10}$) were used; the figures in parentheses are the appropriate dissociation constants K in aqueous solution at 25° (Heilbron and Bunbury, " Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1943), except that for toluene-*p*-sulphonic acid no value was available and the acid was assumed to be of the same strength as benzenesulphonic acid. In aqueous solution the use of these acids would cover a wide range of hydrogen-ion concentrations. The corresponding K's in ethyleneimine solution are not known but, if the various acids are all practically completely dissociated, equivalent concentrations should show similar catalytic effects. This expectation was only partially fulfilled.

General features of the reaction, and evidence for consumption of catalyst. Fig. 2 shows the course of reaction for typical runs with four different acid catalysts. The results are arbitrarily plotted according to equation (2). Two points are to be noted.

First, chloroacetic and toluene-*p*-sulphonic acids have similar catalytic activity, benzoic acid is less effective, and dichlorophenol less again, *i.e.*, the sequence is similar to that of the acid strengths in aqueous solution. Further, phenol, an even weaker acid, shows hardly any catalytic activity (cf. p. 2576); and water, which presumably promotes polymerization (at higher temperatures) by acting as an extremely weak acid, produces no detectable reaction rate at 40°. [It may be noted that water does not seem to be a necessary co-catalyst for other acids, as appears to be the case with certain ionic vinyl polymerizations (cf. Pepper, *loc. cit.*); reactions catalyzed by chloroacetic or toluene-*p*-sulphonic acids were carried out with the specially dried ethyleneimine and with 3% of added water, and the reaction rates agreed within experimental error.]

Secondly, the reaction curves in Fig. 2 all show a progressively decreasing slope, the decrease being particularly pronounced in the early stages (cf. Fig. 1). This effect is definitely not due to some sort of physical adjustment, since ethyleneimine without a

catalyst does not show any volume change over long periods at 40°. It is therefore necessary to reject either assumption (*b*) or assumption (*d*) (see p. 2569) and assume instead (*e*) that the amino-nitrogen atoms in the polymer are of greater basicity than the imino-nitrogen atoms in monomer or polymer, and compete effectively for protons which would otherwise activate imino-rings, or (*f*) that the catalyst is consumed during the reaction. The rejection of assumption (*a*) does not help, since a considerable decline in rate takes place before more than a small fraction of the ethyleneimine has reacted (cf. Fig. 3).

Assumption (*e*) seems ***a priori*** unlikely; although ethyleneimine in aqueous solution is a weaker base than most aliphatic amines, the acid or basic character of a group in a polyacid or polybase is generally less pronounced than that of the same group in the monomeric analogue [*i.e.*, poly(ethyleneimine) would be a weaker base than, say, dimethylamine], and the range of basic strengths of substances in non-aqueous media is small compared with that in aqueous solutions (cf. Hall, *J. Amer. Chem. Soc.*, 1930, **52**, 5115). Nevertheless experiments were carried out. The chloroacetic acid-catalyzed polymerization of ethyleneimine in the presence of 10—15% of initially added bases (ethyleneimine

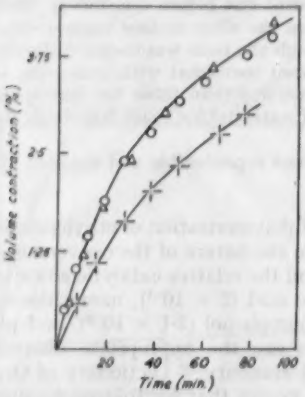


FIG. 3. *Consumption of catalyst during reaction at 40°, with initially 3·2% (by wt.) of chloroacetic acid.*

○, i; △, ii; +, iii (see below).

dimer, *n*-butylamine, or piperidine) was compared with a similar run in the absence of added amines. (If ethyleneimine is an abnormally weak base even in non-aqueous media, the addition of other bases should retard the reaction considerably.) Butylamine and piperidine showed only very small retarding effects which could be attributed to the dilution of the ethyleneimine. Fig. 3 shows the course of reaction, at the same initial acid concentration, for (i) ethyleneimine alone, (ii) ethyleneimine plus 10% of dimer, (iii) as (i) but recalculated by taking the new zero time as the time when 10% of ethyleneimine had been converted into dimer. If there were no destruction of catalyst, (ii) and (iii) should coincide. In actual fact, (i) and (ii) coincide reasonably but (iii) is much slower. It follows that the retardation in the early stages of reaction is not due to dimer formation but must be caused by a decrease in catalyst concentration.

This consumption of the acid catalyst is not surprising. It is known that hydrochloric and sulphurous acid, both of which polymerize ethyleneimine, can also give 2-chloroethylamine and taurine respectively (Gabriel, *Ber.*, 1888, **21**, 1049, 2664), and similar reactions can presumably occur with other acids. Jones *et al.* (*loc. cit.*) had already tentatively suggested that the consumption of acid was responsible for the rapid decrease of the polymerization rate in dilute hydrochloric acid.

To analyze the reaction rates further it is important to bear in mind that the molecular-weight distribution at a given conversion is independent of the nature or concentration of the acid catalyst; the relative distribution of protons amongst the various basic centres (*i.e.*, imino-nitrogen in monomer and polymer; primary and secondary aminonitrogen in polymer) is therefore also the same. Consequently at any given stage of conversion the

rate of reaction (between a charged and an uncharged imine-ring) will be proportional to the concentration of available protons.

We may write

$$-d[M]/dt = \sum^{x,y} k_{xy}[M_x][M_yH^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where M_x represents an uncharged ethyleneimine-ring with a " tail " whose DP is $(x - 1)$ and M_yH^+ a charged ethyleneimine-ring with a " tail " of DP $(y - 1)$; [M] represents the total concentration of imine-rings, both charged and uncharged. The ratio $[M_yH^+]/\sum BH^+$, where B is any basic centre, will be determined only by the extent of conversion of the reaction mixture, and is independent of the nature and concentration of the catalyst.

Effect of initial acid concentration on reaction rate. Results for four different acid catalysts at 40° are shown in Figs. 4—7. The percentage volume contraction is plotted against the function

$$[\text{time} \times \text{catalyst concentration (wt. \%)}]/(\text{dilution factor})$$

where the dilution factor $= 1 + (0{\cdot}01 \times$ the percentage concentration of catalyst, is introduced as a rough compensation for the reduction in *initial* ethyleneimine concentration by the added catalyst; the factor was always less than 1·15.

FIG. 5. FIG. 4.

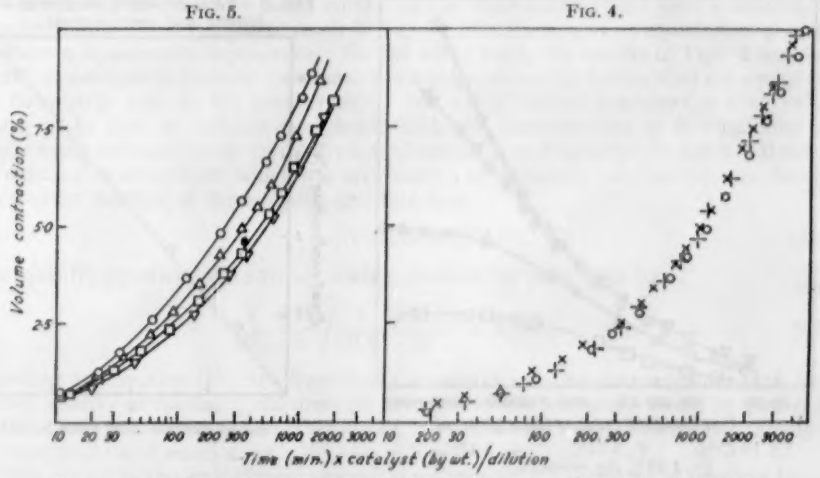


FIG. 4. *Dependence of reaction rate on initial chloroacetic acid concentration at 40°.*
○, 6·01%; △, 3·85%; □, 2·30%; ▽, 1·30% (by weight).

FIG. 5. *Dependence of reaction rate on initial toluene-p-sulphonic acid concentration at 40°.*
○, 9·23%; +, 3·81%; ×, 0·75% (by weight).

(a) *Toluene-p-sulphonic acid.* Fig. 5 shows that results obtained over a 13-fold variation in initial toluenesulphonic acid are very satisfactorily represented by a single curve, so although catalyst is consumed during the reaction, the rate is at all times proportional to the initial acid concentration $[HA]_0$:

$$-d[M]/dt \propto [HA]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The similarity in catalytic activity of chloroacetic and toluene-*p*-sulphonic acid (Fig. 2) suggests that both these acids are practically completely ionized in ethyleneimine. Consequently $\Sigma[BH^+] = [HA]$, the acid concentration at time *t*. Now as $[M_yH^+]/\Sigma[BH^+]$ is independent of acid concentration

$$[M_yH^+] \propto [HA] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

and from (4) and (6),

$$-d[M]/dt \propto [HA] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

(c) *Benzoic acid.* Fig. 6 shows the dependence of rate on initial benzoic acid con-

i.e., the rate at time t is proportional to the acid concentration at that moment. For (5) and (7) to hold simultaneously, the fractional decrease in acid concentration must bear a constant ratio to the fractional decrease in monomer concentration [M], *i.e.*,

$$\frac{1}{[M]}\frac{d[M]}{dt} \Big/ \frac{1}{[HA]}\frac{d[HA]}{dt} = K \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Combining (7) and (8), we have $-d[HA]/dt \propto [HA]^2$ . . . . . (9)

This second-order dependence accords with a consumption of acids by the reaction

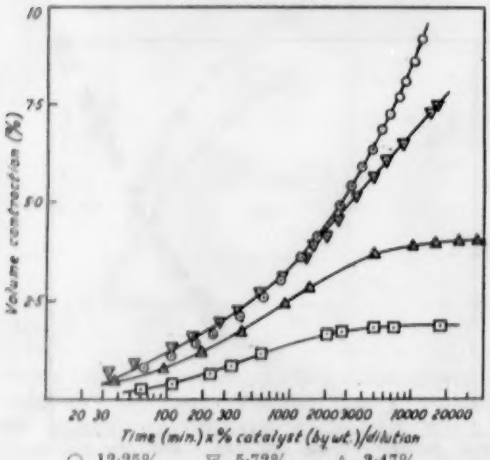
$$\overline{CH_2{\cdot}CH_2{\cdot}N^+H_2} + A^- \longrightarrow A{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (v)$$

and by analogous reactions of A^- with polymer cations. From (v),

$$-d[HA]/dt = \sum^{y} k_{y,A^-}[A^-][M_yH^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

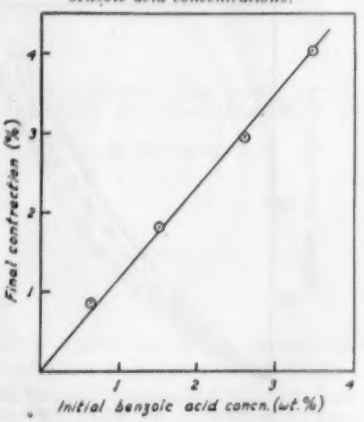
Now $[A^-] = [HA]$ and $[M_yH^+] \propto [HA]$; therefore, from (10), equation (9) follows. We conclude that the kinetics of the polymerization catalyzed by toluene-*p*-sulphonic acid are

FIG. 6. *Dependence of reaction rate on initial benzoic acid concentration at 40°.*



○, 12·25%. ▽, 5·72%. △, 3·47%.
⊡, 1·53% (by weight).

FIG. 7. *Total amount of reaction at low benzoic acid concentrations.*



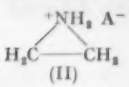
fully understandable in terms of acid consumption by reaction (v), giving products analogous to those prepared with hydrochloric and sulphurous acid (cf. p. 2572).

The observations by Jones *et al.* (*loc. cit.*) that the hydrochloric acid-catalyzed polymerization is of an apparently very high initial order with regard to ethyleneimine but that the half-life is inversely proportional to the initial acid concentration, are exactly analogous to the present (more detailed) results on the toluene-*p*-sulphonic acid system. There is little doubt, therefore, that the same explanation of the kinetics holds in both cases, particularly as in the hydrochloric acid case 2-chloroethylamine is known to be formed [cf. reaction (v)].

(b) *Chloroacetic acid.* Fig. 4 shows results over an approximately five-fold range of chloroacetic acid concentrations, plotted in the same way as in Fig. 5. The state of affairs is less simple than for toluene-*p*-sulphonic acid, as the rate is somewhat more than first-order with regard to initial acid concentration. A complicating factor is the possible reaction $\overline{CH_2{\cdot}CH_2{\cdot}NH} + Cl{\cdot}CH_2{\cdot}CO_2H \longrightarrow \overline{CH_2{\cdot}CH_2{\cdot}N{\cdot}CH_2{\cdot}CO_2H} + HCl$. Thus there may be three different acid species present at any one time, all with their own characteristic rate of destruction by reaction (v). In view of this, a more detailed kinetic analysis of the catalysis by chloroacetic acid was not attempted.

(c) *Benzoic acid.* Fig. 6 shows the dependence of rate on initial benzoic acid concentration. Here the state of affairs is strikingly different from that in Figs. 4 and 5 and the overall rate is clearly greater than first order with respect to initial acid concentration. The divergence is particularly pronounced in the later stages of reaction, where the runs at low benzoic acid concentration practically stop even though most of the ethyleneimine has still not reacted. The final total amount of reaction can, in these cases, be accurately estimated and is accurately proportional to the initial acid concentration (see Fig. 7).

In attempting to explain the results in Figs. 6 and 7, it is necessary also to recall the data of Fig. 2, showing that the catalytic action of benzoic acid is much less than that of stronger acids, even in the initial stages of reaction. For the stronger acids we have assumed complete dissociation, thus *e.g.*, $\overbrace{CH_2{\cdot}CH_2{\cdot}NH} + HA \longrightarrow \overbrace{CH_2{\cdot}CH_2{\cdot}N^+H_2} + A^-$. To account for the lower catalytic activity of a weak acid, we may write the above reaction as an equilibrium, and assume a considerable amount of undissociated HA to be present; or we can assume that with a weak acid an ion-pair complex (II) rather than free ions are formed, and that the catalytic activity of such an ion-pair (*i.e.* its tendency to ring-rupture) is less than that of a free iminium ion. The possibility of such ion-pairs' participating in ionic vinyl polymerizations has been discussed occasionally (cf. Pepper, *loc. cit.*, p. 103).



(II)

Various reaction schemes based on the first of these assumptions were examined, but none explained the simple linear result in Fig. 7; introduction of an equilibrium generally produces a square-root dependence. On the other hand, the results of Figs. 6 and 7 are readily understood in terms of the second assumption, assuming further that the equilibrium lies completely over to the ion-pair side. For $-d[M]/dt$ the treatment is then exactly analogous to that for toluene-*p*-sulphonic acid, the concentration of free iminium ions simply being replaced by the concentration of ion-pairs, and equation (7) holds. However, the destruction of catalyst, which was previously a second-order reaction (v), now becomes a first-order reaction of the ion-pair, and therefore

$$-d[HA]/dt \propto [HA] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Consequently equation (8) for strong acids is replaced for weak acids by

$$\frac{1}{[M]}\frac{d[M]}{dt} \Big/ \frac{1}{[HA]}\frac{d[HA]}{dt} = K[HA] \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

According to equation (12), the fractional decrease in catalyst concentration (and hence in rate) relative to the fractional decrease in monomer concentration would be greater the lower the acid concentration; in other words, the initial rate would decline most rapidly for the most dilute acid solution, as is the case in Fig. 6.

With regard to the limited total amount of reaction ($\Delta[M]$) occurring at very low benzoic acid concentrations (Fig. 7), we assume that, because the conversion of ethyleneimine is very small, reactions of polymeric products can be neglected. We then have:

(i) Monomer consumed by

$$\overbrace{CH_2{\cdot}CH_2{\cdot}N^+H_2}\}A^- + \overbrace{CH_2{\cdot}CH_2{\cdot}NH} \longrightarrow NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overbrace{N^+H{\cdot}CH_2{\cdot}CH_2}\}A^-$$

$$\text{Rate} = k[M][HA] = -d[M]/dt \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

where [HA] = total acid concentration = concentration of ion pairs.

(ii) Acid consumed by $\overbrace{CH_2{\cdot}CH_2{\cdot}N^+H_2}\}A^- \longrightarrow NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}A$

$$\text{Rate} = k'[HA] = -d[HA]/dt \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

Hence $$d[M]/d[HA] = k[M]/k' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

Since [M] remains practically constant in the experiments of Fig. 7, we have from (15)

$$\Delta[M]/\Delta[HA] = k'' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

As all the acid is finally consumed, it follows from (16) that

$$\underset{t\to\infty}{\Delta[M]} = k''[HA]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

i.e., the total monomer consumption is proportional to the initial acid concentration, as found (Fig. 7).

It is concluded that the assumption of ion-pairs rather than of free ions fully explains the differences in kinetic behaviour between the strong toluene-*p*-sulphonic acid and the weak benzoic acid. It is possible that the data in Fig. 5 indicate chloroacetic acid to be an intermediate case.

(d) 2 : 4-*Dichlorophenol.* In aqueous solution this is an even weaker acid than benzoic acid. Fig. 8 illustrates its catalytic effect on the polymerization of ethyleneimine, plotted as for the other acids. The rate is slower than with an equivalent concentration of benzoic acid (cf. Fig. 2), but the nature of the reaction curves is the same (cf. Figs. 6 and 8), and the interpretation suggested for benzoic acid presumably applies, with different velocity constants, to 2 : 4-dichlorophenol also.

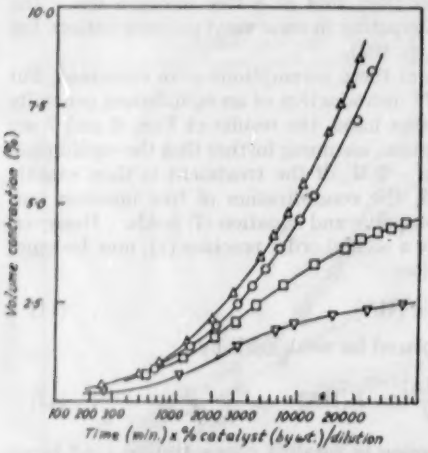


FIG. 8. *Dependence of reaction rate on initial* 2 : 4-*dichlorophenol concentration at* 40°.

△, 14·3%.
○, 8·55%.
□, 4·52%.
▽, 2·17% (by weight).

(e) *Phenol.* Early experiments employing phenol proved very irreproducible. A stock solution of phenol in chloroform was used; the reaction rate at a given phenol concentration, though always very slow, increased with the age of this solution. This effect was ascribed to the production of hydrogen chloride by decomposition of the chloroform; traces of this strong acid would give pronounced effects compared to the very slight activity of phenol. In confirmation, the use of stock solutions of phenol in ether gave reproducible rates which were somewhat lower than if a freshly prepared chloroform solution was used, and much lower than if the solution in chloroform was old.

No comparable difficulty was encountered with other acid catalysts; ether, acetone, and chloroform solutions all gave similar results. Phenol is a particularly unfavourable case in that its catalytic activity is very slight (at 40° ethyleneimine containing 9% of phenol contracts by 1·4% in 300 hrs. compared with 90 min. for 2 : 4-dichlorophenol). Further, the material separates as a liquid when the solvent is pumped off, and is therefore more likely to retain hydrogen chloride than a crystalline acid residue would be.

The detailed kinetics of the phenol-catalyzed reaction were not examined.

The results of Kern and Feuerstein (loc. cit.). Two phenomena observed by these authors (cf. p. 2564) require brief mention here. First, an examination of their rather limited data on the reaction in the presence of sulphanilic acid show a reaction course very similar to that observed here with toluene-*p*-sulphonic acid. Secondly, the explosive course of the reaction at high temperatures and catalyst concentrations is almost certainly due to inadequate dissipation of the heat of polymerization at high rates of reaction.

Summary.—Although the polymerization of ethyleneimine is an addition polymerization, it differs from a vinyl addition polymerization (radical or ionic) in two fundamental respects. First, the existence of a " transfer equilibrium " entails that all monomer *and polymer* molecules are potentially capable of activation or deactivation, and thus produces certain kinetic features similar to those of condensation polymerizations. Secondly, the fractional consumption of catalyst is generally greater than that of monomer, whereas in other polymerizations the reverse tends to be the case; the detailed kinetics of monomer conversion are therefore largely determined by the kinetics of catalyst destruction, and hence may vary from one catalyst to another.

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MAIDENHEAD, BERKS. [*Received, December 29th*, 1954.]

Some Aspects of the Polymerization and Depolymerization of N-*Substituted Ethyleneimines.*

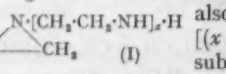
By W. G. BARB.

[Reprint Order No. 51012.]

The polymerization of *N*-substituted ethyleneimines is discussed with special reference to *N*-(2-aminoethyl)ethyleneimine; the products of this polymerization have been examined paper-chromatographically, and by the formation of *o*-chlorobenzoyl derivatives. The latter are 1 : 1 compounds; it is also shown that poly(ethyleneimine) forms a 1 : 1 derivative, and that both polymers must therefore be linear.

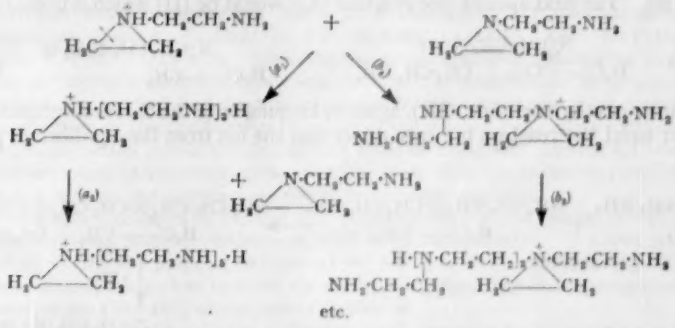
The thermal degradation of some *N*-substituted poly(ethyleneimines) has been examined; in certain cases high yields of the corresponding *NN'*-disubstituted piperazine are obtained. The polymers appear to be less thermally stable than the corresponding ethyleneimine monomers.

BARB (preceding paper) pointed out that in the acid-catalyzed polymerization of ethyleneimine growth reactions could occur not only between polymer and monomer, but also between polymer and polymer. An ethyleneimine polymer [$(x + 1)$-mer] (I) can be regarded as a special case of an *N*-substituted ethyleneimine, and *N*-substituted ethyleneimines are known to polymerize.



(I)

Consideration of the simplest case, the acid-catalyzed reaction of two ethyleneimine-dimer [*i.e.*, *N*-(2-aminoethyl)ethyleneimine] molecules, shows two possible courses of reaction, depending on whether the (hypothetical intermediate) carbonium ion attaches itself to amino- (*a*) or imino- (*b*) nitrogen :



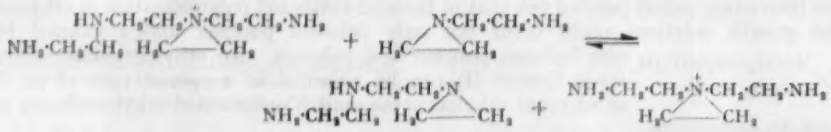
In case (*a*), the dimer of ethyleneimine-dimer is identical with the tetramer of ethyleneimine monomer, the trimer is identical with the hexamer of ethyleneimine, etc. (the protons

will be in equilibrium between all the basic entities). If the reaction follows course (*b*), the polymers are quaternary iminium ions. We may regard (*b*) as the fission of an iminium ring and addition of the carbonium ion so formed to the nitrogen of another ring (without necessarily implying that the reaction occurs in two successive steps); in (*a*), on the other hand, addition occurs at a nitrogen in the side-chain. Whereas course (*b*) is always possible, (*a*) would not be expected to occur unless the *N*-substituent of the particular ethyleneimine had a nucleophilic centre of some sort.

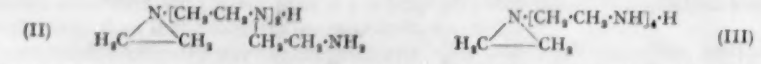
Attempts to decide between (*a*) and (*b*) were made in two ways: (i) a paper-chromatographic examination of the products, and (ii) benzoylation of the polymers and analysis of the product so obtained. As will be shown below, the evidence from these two approaches, though in each case clear-cut, is contradictory and suggests that the actual mechanism is a hybrid of (*a*) and (*b*).

Paper-chromatography.—The technique used has been described (Barb, *loc. cit.*). The chromatogram of the product of a polymerization of the dimer (chloroacetic acid as catalyst) was compared with a similarly prepared polymer of ethyleneimine monomer. The positions and colours of the spots of the unpolymerized dimer and of the first polymerization product of ethyleneimine agree. However, the "dimer of the dimer" occurs at the same position as the ethyleneimine trimer and the "trimer of the dimer" coincides with the pentamer of the monomer. Further comparison of spots was impossible owing to inadequate separation, but from the observations cited it is clear that the "dimer-polymers" are not identical with the ethyleneimine polymers of even degree of polymerization; consequently the polymerization of the dimer undoubtedly does not occur entirely as in (*a*), and we must consider (*b*) in more detail.

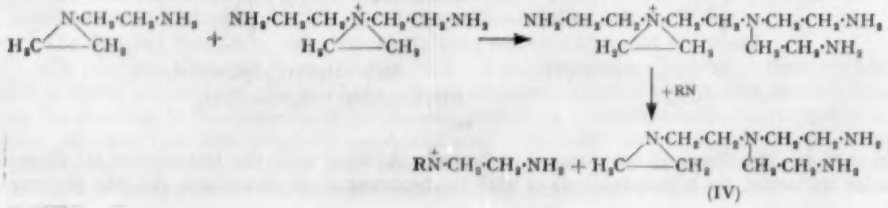
It is extremely unlikely that all the products of the dimer-polymerization are present as quaternary iminium ions. First, the amount of catalyst used is very small, *i.e.*, there would not be one ion available per polymer molecule; secondly, chromatographic comparison of samples taken from a reaction mixture at different times show that the reaction is "stepwise," as in polymerization of the monomer (cf. Barb, *loc. cit.*). These facts suggest that there may be a carbonium-ion equilibrium between active ions and inactive molecules, thus:



This equilibrium would take the place of the hydrogen-ion equilibrium involved in the polymerization of the monomer (cf. Barb, *loc. cit.*). The lowest uncharged polymer which would be formed in the polymerization of the dimer would therefore be identical with ethyleneimine trimer; from this point of view the chromatographic results support mechanism (*b*). The next species [see reaction (b_2)] would be (II) which is isomeric with the



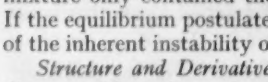
linear pentamer of ethyleneimine, (III), again in keeping with the chromatographic findings. On the other hand the reaction between dimer and the ion from the equilibrium postulated above, *viz.*,



would eventually lead to a tetramer (IV). The chromatograms, however, show no trace of a tetramer. We must therefore conclude that neither mechanism (*a*) nor (*b*) fully explains the chromatographic results.

It seemed of interest to test whether this type of equilibrium was only established with ethyleneiminium ions or whether quaternary ammonium ions showed a similar behaviour. Mixtures of tetramethylammonium bromide and triethylamine in alcohol–water solution were kept at 40° for several days and then examined by paper-chromatography, with butanol saturated with water as a running medium. The spots were developed with Dragendorff's reagent for alkaloids, prepared according to Welcher ("Chemical Solutions," D. Van Nostrand Co., Inc., New York, 1942, p. 119); markers of tetramethyl- and tetraethyl-ammonium bromide, trimethylamine and triethylamine gave spots of characteristic colours (chestnut, deep cerise, vermilion, and pink, respectively). It was found that the mixture only contained the original starting materials; no equilibrium had been set up. If the equilibrium postulated for iminium ions is correct, it would be another manifestation of the inherent instability of these ions.

Structure and Derivatives of Ethyleneimine Polymers.—The polymer of ethyleneimine-dimer could in theory have a linear or a branched structure. The same applies to the polymer obtained from ethyleneimine monomer, as is easily shown by writing the various possible reactions.[7] If in actual fact the polymers are of a completely linear structure (I), acylation or benzoylation of a polymer of high degree of polymerization should give a 1 : 1 derivative (neglecting the imino-end group). If the polymers are branched, there will be less than one acid group per base molecule of ethyleneimine; for the limiting case of a dimer-polymerization occurring as in case (*b*) originally discussed, the polymer would have the structure (V) and the acyl derivative would have a 1 : 2 composition.


(V)

Existing data on derivatives of poly(ethyleneimine) itself are contradictory. Kern and Brenneisen (*J. prakt. Chem.*, **1941**, **159**, 193) acetylated poly(ethyleneimine) in pyridine solution, and purified the water-soluble *N*-acetylpoly(ethyleneimine) by electrodialysis; the compound was of a 1 : 1 composition. Benzoylation and *o*-bromobenzoylation of poly(ethyleneimine) in pyridine, on the other hand, gave compounds containing too much nitrogen and insufficient halogens compared to a 1 : 1 derivative; the purification of these compounds was described as difficult, but no details were given. Using the Schotten–Baumann method, Jones, Langsjoen, Neumann, and Zomlefer (*J. Org. Chem.*, **1944**, **9**, 125) prepared a 1 : 1 polybenzamide, in contrast with Kern and Feuerstein's non-stoicheiometric derivative.

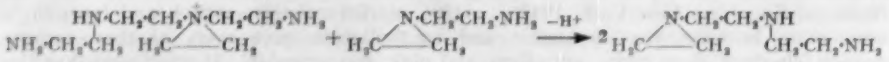
In the present work, poly(ethyleneimine) was made to react with *o*-chlorobenzoyl chloride and *o*-bromobenzoyl bromide, using the procedure described by Jones *et al.* (*loc. cit.*). The derivatives were dried *in vacuo* at room temperature for 18 hr., and contained more halogens and less nitrogen than corresponded to a 1 : 1 compound [*e.g.*, *o*-chlorobenzamide of poly(ethyleneimine) : Found : C, 53·9; H, 4·2; N, 6·65; Cl, 24·45. Calc. for C_9H_8ONCl : C, 59·2; H, 4·95; N, 7·65; Cl, 19·5%]. Since there is no possibility of introducing more than one benzoyl group per nitrogen atom this result was attributed to retention in the polymer of chloroform from which the product had been precipitated by light petroleum; in confirmation, an electrometric titration of the combustion products of the *o*-bromobenzamide with silver nitrate showed a double-inflection curve, indicating that both bromide and chloride ion were present. In view of this retention of solvent there seems little doubt that the anomalous analyses of Kern and Feuerstein's benzoyl derivatives were due to retention of pyridine.

Further attempts to obtain a solvent-free polymer were made, using the more volatile methylene dichloride in place of chloroform, with little improvement. A slight improvement was achieved by drying the polymer *in vacuo* at 60° for 24 hr. The analyses (C, 53·7; H, 4·7; N, 7·0%) are now reasonably close to those for a 1 : 1 compound, the discrepancy corresponding to the retention of less than 10% of methylene dichloride.

The *o*-chlorobenzamide of a polymer of the dimer was prepared by the same procedure. The analyses (C, 51·8; H, 4·8; N, 7·0%) are (except for C) almost identical with those for the derivative of ordinary poly(ethyleneimine), and indicate the compound to be a 1 : 1 derivative.

Since dibenzoylation of primary amino-groups is, under the mild conditions here employed, extremely unlikely, it must be concluded that the " dimer-polymer " has a linear structure, as would be expected from reaction (*a*).

This conclusion of a linear structure for the dimer-polymer is in direct conflict with the chromatographic results, which indicate that the " dimer-polymers " correspond to ethyleneimine polymers of odd degree of polymerization. The only mechanism embracing all the experimental results is that the first step in the polymerization of dimer occurs as in (b_1); the ion so formed then undergoes the reaction :



to yield the trimer, and subsequent growth of the polymer occurs by reaction of type (*a*). The theoretical justification for this transition from one type of reaction to another is not obvious.

Depolymerization of N-*Substituted Ethyleneimines.*—In some experiments on the polymerization of *N*-phenethylethyleneimine, prepared according to Bestian (*Annalen*, 1950, **566**, 210), it was found that if the gummy polymer was heated in a sealed tube at 150° for several hours, the initially brownish material was almost completely converted into a mobile pale amber liquid, which was immiscible with traces of residual polymer and completely set to a crystalline mass on cooling. The material was extremely soluble in most solvents but could be recrystallised from light petroleum (b. p. 40—60°) to give small white crystals, m. p. 80°. The substance was surmised to be 1 : 4-*di*(*phenethyl*)*piperazine*. This compound was prepared from phenethyl bromide and piperazine [by the method employed by Gabriel and Stelzner (*Ber.*, 1896, **29**, 2384) to prepare the corresponding benzyl compound], m. p. 79—80°; mixed with the pyrolytic material, m. p. 79—80° (Found : Synthetic compound : C, 80·6; H, 8·8; N, 9·8; Pyrolytic compound : C, 81·2; H, 8·8; N, 9·4. $C_{10}H_{12}N$ requires C, 81·6; H, 8·85; N, 9·55%). It is particularly interesting that *N*-(phenethyl)ethyleneimine monomer heated under similar conditions to those employed above showed no change. The polymer is thus thermally *less* stable than the " strained " three-membered ring, possibly owing to the increase in entropy which accompanies the degradation of the polymer to small molecules.

Other polymers examined showed a less clear-cut degradation; the ease of depolymerization and the amount of side-reactions evidently varies greatly with the nature of the N-substituent. A polymer of *N*-(2-cyanoethyl)ethyleneimine, prepared according to Bestian (*loc. cit.*), set to a solid black tar when heated to 200°; further heating, at 280° for four hours, produced a small amount of a mobile liquid which did not crystallize on cooling, but a far-reaching decomposition seemed to have occurred since the tube exploded on being cut open. Similarly poly(ethyleneimine) had to be heated to about 280° before a small amount of a mobile product was formed; this partially crystallized on cooling and was presumably piperazine, but again other decompositions must have occurred since the reaction tubes invariably exploded when cut open. The work of Hutchinson, Collett, and Lazzell (*J. Amer. Chem. Soc.*, 1945, **67**, 1967) on the pyrolysis of polyamines illustrates the variety of compounds which might be formed from poly(ethyleneimine).

Poly-(*N*-*n*-butylethyleneimine) proved a more favourable case. When the polymer was heated at 200° for a few hours about one-half of the material was converted into a yellow mobile liquid, immiscible with the residual polymer. After redistillation in a high vacuum, the product was colourless (n_D^{15} 1·4586). For comparison, 1 : 4-di-*n*-butylpiperazine was synthesized from *n*-butyl bromide and piperazine by Gabriel and Stelzner's method (*loc. cit.*); it was a clear viscous liquid, b. p 110°/8 mm., n_D^{15} 1·4582, in excellent agreement with the value for the pyrolytic material.

Attention is drawn to the close analogy between the depolymerization reactions here described and the decomposition of polysarcosine to 1 : 4-dimethyldioxopiperazine (" sarcosine anhydride "), discovered by Wessely and Sigmund (*Z. physiol. Chem.*, 1927, **159**, 192).

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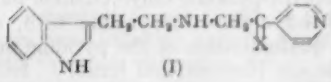
An Attempt to Simulate the Biogenesis of Strychnine. Part I. Experiments with 4-2′-Aminoethylpyridine.

By A. R. Katritzky.

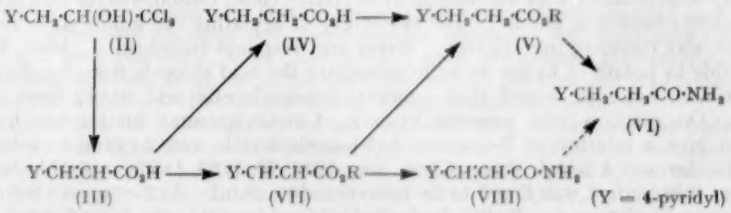
[Reprint Order No. 6141.]

The preparation of 4-2′-aminoethylpyridine has been carefully investigated. A variety of derivatives of 3-indolylacetic acid and its 1-methyl analogue is described, but all attempts to condense the above-mentioned amine with these acids have failed.

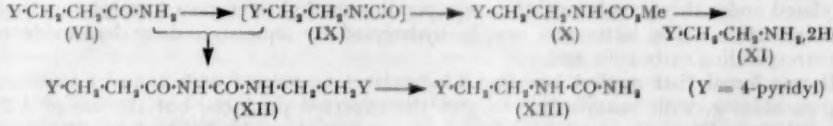
Robinson and Saxton (*J.*, 1953, 2598) pointed out that a synthesis of strychnine, closely following the biogenesis, might be realised in a very simple manner from the pyridine derivative (I; X = :CH·CH_2·OH). Possible routes to this compound and to its simpler analogue (I; X = H_2) have been under investigation. This paper deals with the preparation of 4-2′-aminoethylpyridine and its attempted conversion into the latter compound.



(I)



An improved version of Kleiman and Weinhouse's directions (*J. Org. Chem.*, 1945, **10**, 562) for conversion of 4-(3 : 3 : 3-trichloro-2-hydroxypropyl)pyridine (II) into β-4-pyridylacrylic acid (III) is given in the Experimental section. Walter, Hunt, and Fosbinder (*J. Amer. Chem. Soc.*, 1941, **63**, 2771) have briefly described the conversion of this compound into β-4-pyridylpropionamide (VI) by way of the saturated acid (IV) and ester (V). These intermediates have now been characterised and alternative routes to the amide investigated. Direct esterification of β-4-pyridylacrylic acid afforded the methyl and the ethyl ester (VII), but these reacted only slowly with aqueous ammonia to give the amide (VIII). Reduction of ethyl β-4-pyridylacrylate (VII) gave the saturated ester (V), but the overall yield was lower than that obtained by reduction at the acrylic stage.



The amide (VI) was reported (Walter *et al.*, *loc. cit.*) to be converted by a Hofmann reaction in methanol, *via* the oily urethane (X), into 4-2′-aminoethylpyridine dihydrochloride (XI). When a suspension of the amide (VI) was treated slowly with bromine at 0° according to the published directions, in place of the expected urethane (X), a new crystalline compound was obtained in 92% yield. It is known that attempted Hofmann reactions sometimes lead to the formation of ureas (*Organic Reactions*, 1946, **3**, 269) and this compound was proved to be *N*-(2-4′-pyridylethyl)-*N*′-(β-4-pyridylpropionyl)urea (XII) [formed by reaction of the intermediate *iso*cyanate (IX) with unchanged amide] by hydrolysis to 4-2′-ureidoethylpyridine (XIII).

In the aliphatic series, formation of a urea in Hofmann reactions may be avoided by

working in methanol and adding the bromine rapidly (*ibid.*, p. 282). With β-4-pyridylpropionamide results were erratic; three experiments gave the oily urethane whence 4-2′-aminoethylpyridine dihydrochloride was obtained in good yield, but another under apparently the same conditions gave the urea (XII), possibly owing to variation in pH caused by not using sodium methoxide and bromine in exactly equivalent quantities.

Treating the hydrochloride with aqueous sodium hydroxide and ether gave three liquid layers, and so 4-2′-aminoethylpyridine could not be obtained quite pure. The free base would be expected to lose ammonia easily, for the amino-group is activated in much the same way as in a β-amino-ketone. It was characterised as a mono- and a di-picrate and underwent normal acylation with benzoyl chloride and toluene-*p*-sulphonyl chloride.

Goldschmit and Lautenschlager's method (*Annalen*, 1953, **580**, 74) of preparing amides from amines and acids seemed particularly suitable for the preparation of acylated derivatives of 4-2′-aminoethylpyridine because the amine (and/or acid) may be used as hydrochloride. In an assessment of the utility of the phosphoroazo-reaction, *N*-benzoylbenzylamine, *N*-phenylacetylbenzylamine, and *N*-benzoyl-2-phenylethylamine were obtained in excellent yield. 4-2′-Benzamidoethylpyridine and 4-2′-phenylacetamidoethylpyridine were prepared from 4-2′-aminoethylpyridine dihyrochloride but in lower yield.

The direct alkylation of 4-2′-aminoethylpyridine with, *e.g.*, 3-2′-bromoethylindole, would be difficult because of quaternisation of the pyridine nitrogen. 3-Indolylacetaldehyde is difficult to prepare (Brown, Henbest, and Jones, *J.*, 1952, 3172) and the Schiff base formed by condensation with 4-2′-aminoethylpyridine could tautomerise to another which could undergo facile ring closure. The possibility of acylating the amine with an indole derivative was therefore investigated. Baker and Happold (*Biochem. J.*, 1940, **34**, 657) were unable to isolate or to use as an intermediate the acid chloride from 3-indolylacetic acid. It was, however, hoped that 1-methyl-3-indolylacetic acid would form an acid chloride. On reaction with aqueous cyanide, 1-methylgramine methiodide has been shown to give a mixture of 3-cyanomethyl-1-methylindole and 2-cyano-1 : 3-dimethylindole (Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703, 1856), separable by distillation, but this method was found to be tedious and wasteful. As 2-cyano-1 : 3-dimethylindole is very resistant to alkaline hydrolysis (*idem*, *loc. cit.*), the mixed nitriles were hydrolysed directly and 1-methyl-3-indolylacetic acid was isolated in 50% yield.

1 : 3-Dimethylindole-2-carboxylic acid has been converted into its amide by treatment with phosphorus pentachloride and acetyl chloride followed by removal of volatile compounds *in vacuo* and addition of aqueous ammonia (*idem*, *loc. cit.*). An attempt to prepare 1-methyl-3-indolylacetamide by the same procedure gave a mixture. Analytical figures indicated that partial acetylation at the 2-position of the indole nucleus might have been responsible. Experiments with aniline and methylamine gave similar results, but when 4-2′-aminoethylpyridine was used, no solid product was obtained. Magnanini (*Ber.*, 1888, **21**, 1936) has shown that skatole with acetyl chloride and zinc chloride at room temperature gives 2-acetyl-3-methylindole; although 1-methyl-3-indolylacetic acid was not acetylated under these conditions, the corresponding methyl ester gave 2-acetyl-1-methyl-3-indolylacetate. The latter was readily hydrolysed by aqueous sodium hydroxide to the corresponding carboxylic acid.

It was found that methyl 1-methyl-3-indolylacetate reacted with aqueous ammonia and, on heating, with benzylamine to give the expected products, but the use of 4-2′-aminoethylpyridine gave no solid product in three attempts under different conditions.

Acid azides may often be used as acylating agents where sensitive groups in the molecule prevent the formation or use of an acid chloride. Methyl 1-methyl-3-indolylacetate with hydrazine hydrate gave the hydrazide; attempts to form the azide in dilute hydrochloric acid failed, but in aqueous acetic acid the azide was formed, although only as an oil, which soon decomposed. Small amounts of crystalline material of high m. p. were also produced, which were shown to be *NN*′-di-(1-methyl-3-indolylacetyl)hydrazine by treating the hydrazide with half an equivalent of nitrite; the azide then acylated unchanged hydrazide to give this compound in quantity. Benzylamine was smoothly acylated by the azide, but nothing crystalline could be isolated by using 4-2′-aminoethylpyridine.

By the phosphoroazo-method (see above) 1-methyl-3-indolylacetic acid was readily

converted into its anilide, but no crystalline amide could be isolated when 4-2′-aminoethylpyridine dihydrochloride was used.

A methyl group in the 1-position usually lowers the melting point of indole derivatives; as the experiments recorded above appeared to have failed as much from the lack of success in obtaining crystalline intermediates as for any other reason, a similar research starting with 3-indolylacetic acid was carried out. Results were very similar: simpler amines were readily acylated, but attempts with 4-2′-aminoethylpyridine failed. In one run in which the phosphoroazo-method was used, a small quantity of 3-indolylacetamide was isolated; as the mixture was worked up so as to isolate the basic fraction, it appears that this must have been formed by decomposition of the desired 4-(2-3′-indolylacetamidoethyl)pyridine, which is feasible in view of the formal resemblance of 4-2′-aminoethylpyridine to a β-amino-ketone.

While it was still hoped to prepare 4-(2-3′-indolylacetamidoethyl)pyridine by the methods indicated above, the reduction of 3-indolylacetanilide was undertaken as a model. 3-2′-Anilinoethylindole was readily obtained.

Experimental

β-4-*Pyridylpropionamide*.—Potassium hydroxide (96 g.) in ethanol (commercial absolute, 700 c.c), at room temperature, was added to 4-(3 : 3 : 3-trichloro-2-hydroxypropyl)pyridine (96 g.) in ethanol (700 c.c), and the whole warmed cautiously on the water-bath under a single wide reflux condenser, with periodic cooling as necessary. After the first reaction, the mixture was heated for 2 hr., filtered, and distilled under slightly reduced pressure until solid began to separate. Water (400 c.c.) was then added and the distillation continued until most of the ethanol had been removed. Acetic acid (50 c.c) then precipitated β-4-pyridylacrylic acid (average yield in 5 runs 78%), m. p. 289—291° (decomp.). Kleiman and Weinhouse (*loc. cit.*) give m. p. 296° (decomp.). Purification was carried out as described by them.

The above acid (66 g.) in aqueous sodium hydroxide (19 g. in 190 c.c.) was hydrogenated over Raney nickel at 100°/50 atm. (absorption approx. theor.). Addition of acetic acid (29 c.c.) gave β-4-pyridylpropionic acid (55·6 g., 83%), m. p. 214—220°, raised by crystallisation from ethanol to 228—230° (Found: C, 63·5; H, 5·9. Calc. for $C_8H_9O_2N$: C, 63·6; H, 6·0%) (Doering and Weil, *J. Amer. Chem. Soc.*, 1947, **69**, 2465, give m. p. *ca.* 220°; Rubtsov, *J. Gen. Chem. U.S.S.R.*, 1946, **16**, 461, gives m. p. 232°). This acid (10 g.), methanol (30 c.c.), and sulphuric acid (12 c.c.) were heated for 4 hr. on the water-bath, then poured on ice and aqueous ammonia (*d* 0·88; 30 c.c.). The whole was extracted with ether. Distillation of the dried extracts gave the *methyl ester* (8·5 g., 78%), b. p. 128—129°/11 mm. (Found: C, 65·7; H, 6·7. $C_9H_{11}O_2N$ requires C, 65·5; H, 6·7%) (Walter *et al.*, *loc. cit.*, give b. p. 95°/2 mm., but no analysis). The ester with excess of aqueous ammonia at 0° gave the amide (98%), m. p. 165—166° (Walter *et al.* give m. p. 166—167).

β-4-Pyridylacrylic acid (14 g.) was esterified as described above for β-4-pyridylpropionic acid to give the ethyl ester (13·5 g., 81%), m. p. 64·5—66° (from light petroleum) (Found: C, 67·3; H, 6·2. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·2%) (Rubtsov, *loc. cit.*, gives m. p. 67—69°). The *methyl ester*, similarly prepared, separated from light petroleum (b. p. 60—80°) in prisms, m. p. 74—77° (Found: C, 66·6; H, 5·7. $C_9H_9O_2N$ requires C, 66·3; H, 5·5%). These esters with ammonia gave the *amide*, which crystallised from ethanol in plates, m. p. 185—187° (Found: C, 64·7; H, 5·5. $C_8H_8ON_2$ requires C, 64·9; H, 5·4%).

Ethyl β-4-pyridylacrylate (40 g.) in ethanol (25 c.c.) was hydrogenated over Raney nickel at 100°/50 atm. for 24 hr. The mixture was filtered and distilled, to yield *ethyl β-4-pyridylpropionate* (26 g., 62%), b. p. 133°/9 mm., n_D^{20} 1·4968 (Found: C, 67·0; H 7·6. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%).

4-2′-*Ureidoethylpyridine*.—β-4-Pyridylpropionamide (6 g.) was added to a cold solution of sodium (1·84 g.) in methanol (60 c.c.), the whole cooled to < 0°, and bromine (6·4 g.) dropped in during 10 min. with vigorous stirring. The whole was refluxed for 1 hr., methanol removed on the water-bath, and water (30 c.c.) added. *N-2-4′-Pyridylethyl-N′-β-4-pyridylpropionylurea* separated and more was obtained by extraction of the mother-liquor with chloroform (total yield 5·5 g., 92%). The compound was obtained from ethanol–water (1 : 1) as prisms, m. p. 144—146° [Found: C, 64·2, 64·4; H, 6·1, 6·2%; *M* (Rast), 312. $C_{15}H_{18}O_2N_4$ requires C, 64·4; H, 6·0%; *M*, 298]. The *dipicrate* (from ethanol–benzene) had m. p. 216—217° (Found: C, 44·7; H, 3·4. $C_{28}H_{24}O_{16}N_{10}$ requires C, 44·4; H, 3·2%). This urea (3 g.) was boiled with concentrated hydrochloric acid (12 c.c) for 1 hr., and the whole poured into aqueous sodium hydroxide,

to give 4-2′-*ureidoethylpyridine*, which crystallised from acetone–water (10 : 1) in needles, m. p. 204—205·5° (Found: C, 57·8; H, 6·7; N, 25·4. $C_8H_{11}ON_3$ requires C, 58·2; H, 6·7; N, 25·4%). The *picrate* separated from ethanol–benzene in yellow prisms, m. p. 199—200° (Found: C, 42·6; H, 3·5. $C_{14}H_{14}O_8N_6$ requires C, 42·6; H, 3·5%).

4-2′-*Aminoethylpyridine*.—β-4-Pyridylpropionamide (15 g.) was added to a solution of sodium (4·6 g.) in methanol (150 c.c.) at room temperature, and bromine (16 g.) added all in one lot with good stirring. The mixture became warm and the colour of the bromine soon disappeared; the whole was then refluxed for 30 min., the methanol distilled off, water (50 c.c.) added, and the whole extracted with chloroform (3 × 20 c.c.). Solvent was removed from the dried extracts, the residue refluxed with hydrochloric acid (35 c.c.) for 4 hr. and evaporated to dryness, and the product recrystallised from acetic acid to give the dihydrochloride (15 g., 77%). The m. p. depends on the rate of heating; on immersion at 215° and rapid heating it was 226—229° (Walter *et al.*, *loc. cit.*, give m. p. 222°) (Found: C, 42·9; H, 6·3. Calc. for $C_7H_{12}N_2Cl_2$: C, 43·1; H, 6·2%). The dihydrochloride (5 g.) was mixed with ether (10 c.c.) and aqueous sodium hydroxide (30%; 9 c.c.). Three liquid layers were formed; the upper two were separated, solvent was removed, and the residue distilled *in vacuo*. On redistillation the amine was obtained as a colourless liquid, b. p. 112°/13 mm. Completely satisfactory analytical figures were not obtained for this compound. In ethanol it gave a *monopicrate*, yellow needles, m. p. 153—155° (Found: C, 43·8; H, 3·7. $C_{13}H_{12}O_7N_6$ requires C, 44·4; H, 3·7%), and a *dipicrate*, yellow microcrystalline powder, m. p. 190—192° (Found: C, 39·7; H, 3·1. $C_{19}H_{14}O_{14}N_8$ requires C, 39·9; H, 2·8%). The amine (0·12 g.) in benzene (1·5 c.c.) and triethylamine (0·3 c.c.) was treated with benzoyl chloride (0·16 g.). The resulting solid was extracted with water and recrystallised from benzene to give the *benzoyl derivative* in prisms, m. p. 115—116° (Found: C, 73·9; H, 6·3. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%). The *toluene*-p-*sulphonyl* derivative, similarly prepared, separated from benzene in needles, m. p. 137—138° (Found: C, 60·7; H, 5·9. $C_{14}H_{16}O_2N_2S$ requires C, 60·9; H, 5·8%).

Trial of the Phosphoroazo-method of Amide Formation.—(The pyridine used in these and other examples of the reaction was distilled off solid potassium hydroxide, refluxed for 24 hr. over calcium oxide, and redistilled. The phosphorus trichloride was a redistilled commercial product.) Phosphorus trichloride (0·43 c.c.) was added to benzylamine (1·07 g.) in pyridine (10 c.c.) at 0°. Phenylacetic acid (1·36 g.) was added 30 min. later and the whole heated for 3 hr. at 100°. Pyridine was removed at 100°/12 mm. and the residue triturated with water to give *N*-phenylacetylbenzylamine (2·25 g., 100%), m. p. 109—114°, raised by recrystallisation from ethanol to 120—121° (Weiss, *Monatsh.*, 1919, **40**, 401, gives m. p. 122°). *N*-Benzoylbenzylamine, m. p. 105°, and *N*-benzoyl-2-phenylethylamine, m. p. 114·5—115·5°, were similarly prepared.

Phosphorus trichloride (0·43 c.c.) was added to 4-2′-aminoethylpyridine dihydrochloride (1·95 g.) in pyridine (35 c.c.) at 0°. After 30 min., benzoic acid (1·22 g.) was added, the whole heated 20 hr. at 100°, solvent removed, and aqueous sodium hydroxide and chloroform were added. 4-2′-Benzamidoethylpyridine (1 g., 44%), recovered from the organic layer, had m. p. 112·5—114·5° after recrystallisation from benzene, mixed m. p. (see above) 113·5—115°. 4-2′-*Phenylacetamidoethylpyridine*, similarly prepared (20% yield), separated in prisms (from ethyl acetate), m. p. 83—86° (Found: C, 74·9; H, 6·8. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7%).

1-*Methyl*-3-*indolylacetic Acid*.—1-Methylgramine methiodide (127 g.) was refluxed with potassium cyanide (104 g.) in water (720 c.c.) for 2½ hr. Extraction with ether and removal of solvent from the dried extracts gave the mixed nitriles (61 g., 94%). These (17 g.) were boiled with potassium hydroxide (40 g.) in ethanol (160 c.c.) and water (30 c.c.) for 17 hr. Water (300 c.c.) was added and the mixture distilled to half its volume. Hydrochloric acid was added to give a small permanent precipitate, and the whole boiled for 15 min. with charcoal, filtered and made strongly acid, the acid (9·4 g., 50%) then separating; after two recrystallisations from benzene, the m. p. was 127—128° (Snyder and Eliel, *loc. cit.*, give m. p. 127—128·5°). The picrate separated from benzene in red needles; the m. p. varied with the rate of heating; with immersion at 165° it was 172—172·5° (decomp.) (Piccini, *Atti R. Accad. Lincei*, 1889, **8**, I, 315, records dark red prisms, m. p. 173—174°; Snyder and Eliel, *loc. cit.*, report red needles, m. p. 160·5—161·5°).

Methyl 1-*Methyl*-3-*indolylacetate*.—When prepared by ethereal diazomethane, and isolated (93%) by distillation the *ester* had b. p. 192—193°/16 mm. (Found: C, 71·1; H, 6·6. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4%). After three weeks the oil solidified; the ester separated from ethyl acetate–light petroleum (1 : 5) (cooling in ethanol–solid carbon dioxide) in colourless prisms, m. p. 35—36·5°. A red Ehrlich test was given on warming; the colour faded on cooling. The

picrate separated from benzene in dark red prisms, m. p. 78—80° (Found: C, 50·1; H, 3·7. $C_{18}H_{16}O_9N_4$ requires C, 50·0; H, 3·7%).

2-Acetyl-1-methyl-3-indolylacetic Acid.—The above ester (2 g.) in acetyl chloride (20 c.c.) was stirred for 5 min. with zinc chloride (1 g.) at room temperature, and the whole poured into water to give *methyl 2-acetyl-1-methyl-3-indolylacetate* (2·15 g., 89%), which separated from ethanol in needles, m. p. 113·5—115° (Found: C, 68·8; H, 6·2. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1%). No colour was given with Ehrlich's reagent. This compound (1·75 g.) was boiled with sodium hydroxide (3 g.) in water (20 c.c.) for 15 min. Dilute hydrochloric acid then precipitated the *acid* (1·25 g., 76%) which after three crystallisations from ethanol–water (1 : 1) (charcoal) was obtained in pale yellow plates, m. p. 167—168° (Found: C, 67·4; H, 5·6. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%). No colour was given with Ehrlich's reagent. The *semicarbazone*, prepared in pyridine, separated from ethanol in solvated needles, m. p. 195—197° (decomp.) (Found: C, 57·3; H, 6·4. $C_{14}H_{16}O_3N_4,C_2H_6O$ requires C, 57·5; H, 6·6%).

Acylation with Methyl 1-Methyl-3-indolylacetate.—Keeping the ester in aqueous ammonia for 10 days gave the *amide* which separated from ethanol–water (1 : 1) in needles, m. p. 182—184° (Found: C, 69·7; H, 6·4. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4%). A red Ehrlich test was given on warming. Heating the ester (0·5 g.) with benzylamine (3 c.c.) at 140° for 4 hr., and pouring the whole into dilute hydrochloric acid gave *N-benzyl-1-methyl-3-indolylacetamide* (0·5 g., 72%) which separated from ethanol–water (2 : 1) in needles, m. p. 111—113° (Found: C, 77·4; H, 6·5. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5%). It gave a weak red Ehrlich test on warming.

Acylations with 1-Methyl-3-indolylacetazide.—Methyl 1-methyl-3-indolylacetate (8 g.), hydrazine hydrate (100%, 8 c.c.), and water (12 c.c.) were heated at 100° for 2 hr. to give the *hydrazide* (7·5 g., 94%) which crystallised from ethanol in needles, m. p. 134—136° (Found: C, 65·0; H, 6·7. $C_{11}H_{13}ON_3$ requires C, 65·0; H, 6·4%). An orange-red Ehrlich test was given on warming. This hydrazide with benzaldehyde in warm ethanol gave a *benzylidene derivative*, m. p. 150·5—152·5° (from pentyl alcohol) (Found: C, 74·1; H, 5·9. $C_{18}H_{17}ON_3$ requires C, 74·2; H, 5·8%). Treatment of the hydrazide (0·5 g.) in acetic acid (2 c.c.) and ice (10 g.) with sodium nitrite (0·09 g.), followed, after 5 min., by potassium carbonate solution (2 c.c. of 30%) gave *NN'-di-(1-methyl-3-indolylacetyl)hydrazine* (0·3 g., 65%) which crystallised from pentyl alcohol in needles, m. p. 248—249° (Found: C, 70·7; H, 6·0. $C_{22}H_{22}O_2N_4$ requires C, 70·6; H, 5·9%).

Ice (10 g.) followed by sodium nitrite (0·2 g.) in water (1 c.c.) was added to the hydrazide (0·5 g.) in acetic acid (2·5 c.c.). The azide separated as an oil, and was taken up in chloroform (10 c.c.), and the chloroform layer was quickly dried (Na_2SO_4) and mixed with benzylamine (2 c.c.). After 12 hr., the whole was filtered, solvent removed, and dilute hydrochloric acid added to give *N*-benzyl-1-methyl-3-indolylacetamide (0·52 g., 75%), needles [from ethanol–water (2 : 1)], m. p. 112—113° and mixed m. p. 111—113° with a specimen prepared from the ester.

Acylations with 1-Methyl-3-indolylacetic Acid.—By the standard phosphoroazo-procedure this acid was converted into the *anilide* (73% yield) which separated from ethanol–water (2 : 1) as needles, m. p. 116—117·5° (Found: C, 77·1; H, 6·1. $C_{17}H_{16}ON_2$ requires C, 77·3; H, 6·1%). A deep red Ehrlich test was given on warming.

Experiments with 3-Indolylacetic Acid.—The following derivatives of this acid (prepared by a modification of the method of Snyder and Pilgrim, *J. Amer. Chem. Soc.*, 1948, **70**, 3771) were obtained by methods similar to those described above for their 1-methyl analogues: *methyl 3-indolylacetate* (69%), b. p. 205—208°/10 mm., 216—218°/17 mm., prisms (from ethyl acetate–light petroleum), m. p. 49—50·5° (Found: C, 70·0; H, 5·6. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·8%), giving a cherry-red Ehrlich reaction (Jackson, *J. Biol. Chem.*, 1930, **88**, 659, gives no analysis and describes it as an oil of b. p. "about 180°/2 mm."; Koegl and Kostermanns, *Z. physiol. Chem.*, 1935, **235**, 201, describe it merely as an oil). The orange-red picrate of this ester, crystallised from benzene, had m. p. 125—126° (Koegl *et al.*, *loc. cit.*, give m. p. 125°). *N-Benzyl-3-indolylacetamide* (87% from ester; 73% from the hydrazide *via* the azide; 91% from the acid by the phosphoroazo-method), separated from ethanol–water (2 : 1) in plates, m. p. 152·5—153·5°, and gave a cherry-red Ehrlich reaction (Found: C, 77·3; H, 6·1. $C_{17}H_{16}ON_2$ requires C, 77·3; H, 6·1%). *3-Indolylacethydrazide* (97%) crystallised from ethanol–water (1 : 4) in needles, m. p. 127·5—129·5° and gave a red Ehrlich test (Found: C, 63·3; H, 6·0. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8%). The *benzylidene derivative* of the latter separated from pentyl alcohol in prisms, m. p. 187—188° (Found: C, 73·6; H, 5·6. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4%). *3-Indolylacetanilide* (25% from the hydrazide *via* the azide; 80% from the acid by the phosphoroazo method) crystallised from ethanol–water (2 : 1) in prisms, m. p. 149·5—150°,

and gave a cherry-red Ehrlich test (Found: C, 76·6; H, 5·6. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%). NN'-*Di*-(3-*indolylacetyl*)*hydrazine* (55%) separated from acetic acid in needles, m. p. 229—230° (Found: C, 69·4; H, 5·2. $C_{20}H_{18}O_2N_4$ requires C, 69·4; H, 5·2%).

Attempted Preparation of 4-(2-3'-*Indolylacetamidoethyl*)*pyridine.*—The corresponding acid and amine dihydrochloride were subjected to the standard phosphoroazo-procedure; after 12 hours' heating at 100°, volatile matter was removed at 100°/14 mm. and dilute hydrochloric acid added to the residue to acidity to Congo-red. The whole was extracted 4 times with chloroform, made strongly alkaline, and extracted with ethyl acetate. From the latter extracts was obtained 3-indolylacetamide, m. p. and mixed m. p. 150·5—152° (Found: C, 68·8, 68·8; H, 5·8, 5·7. Calc. for $C_{10}H_{10}ON_2$: C, 69·0; H, 5·7%) (Majima and Hoshino, *Ber.*, 1925, **58**, 2046, give m. p. 150—151°).

3-2'-*Anilinoethylindole.*—3-Indolylacetanilide (2 g.) was refluxed for 24 hr. with lithium aluminium hydride solution (M in ether; 25 c.c.) and ether (80 c.c.). Ethyl acetate to decompose excess of hydride was added, followed by sodium hydroxide (15 g.) in water (40 c.c.). Removal of solvent from the dried ether layer gave the *amine* (0·9 g., 48%) which separated from ethanol–water (2 : 1) in prisms, m. p. 98—100° (Found: C, 81·2; H, 6·9. $C_{16}H_{16}N_2$ requires C, 81·3; H, 6·8%). Carbonyl bands were absent from the infrared spectrum. A cherry-red Ehrlich test was given. The *acetyl derivative* crystallised from ethanol–water (2 : 1) in needles, m. p. 120—121·5 (Found: C, 77·7; H, 6·7. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5%).

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The Dyson Perrins Laboratory, Oxford University. [*Received, February 25th*, 1955.]

An Attempt to Simulate the Biogenesis of Strychnine. Part II. Preparation and Transformations of* 3-(2-4'-*Pyridylacetamidoethyl*)*indole.*

By A. R. Katritzky.

[Reprint Order No. 6163.]

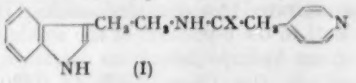
After some unsuccessful attempts, 3-(2-4'-pyridylacetamidoethyl)indole was prepared by condensing methyl 4-pyridylacetate with tryptamine. Pyrolysis of 4-(1-benzoyloxy-1-cyanoethyl)pyridine is shown to involve acyl–oxygen fission. The methiodide of the above indole with alkali gave the anhydro-base, and some transformations of this and analogous compounds are described. An example of the reduction of an αβ-unsaturated amide at the C:C double bond by lithium aluminium hydride is given. A mechanism is advanced for the reduction of pyridinium salts by borohydride to tetrahydropyridines in neutral or weakly acid solution.

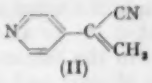
The preparation of the base (I; X = H_2) by reaction of an indole derivative with 4-2'-aminoethylpyridine having failed (Part I *), the preparation of this compound from tryptamine and a pyridine derivative was investigated. Preparation direct from tryptamine, formaldehyde, and, *e.g.*, γ-picoline appeared unpromising because of simultaneous formation of tetrahydrocarboline. It was hoped that 4-diazoacetylpyridine with silver powder and tryptamine would give 3-(2-4'-pyridylacetamidoethyl)indole (I; X = O); but Dornow's preparation of the diazo-ketone (*Ber.*, 1940, **73**, 185) could not be repeated; instead an ether-insoluble, water-soluble tar was obtained; *N*-methylation may have taken place.

Clemo, Morgan, and Raper (*J.*, 1937, 965) reported the preparation of 2-bromoacetylpyridine from 2-acetylpyridine, but when 4-acetylpyridine (prepared by a simplified modification of Kolloff and Hunter's method, *J. Amer. Chem. Soc.*, 1941, **63**, 490) was brominated under the same conditions an addition compound was produced. This changed above its melting point into 4-bromoacetylpyridine hydrobromide, but neither this nor the

* Part I, preceding paper.

free base could be obtained pure and nothing could be isolated after reactions with piperidine or tryptamine. These failures were probably due to quaternisation of the pyridine-nitrogen atom, and in an attempt to brominate a quaternary derivative of 4-acetylpyridine the methobromide was prepared *via* the methiodide, but it was not brominated smoothly in acetic acid.


(I)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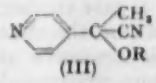
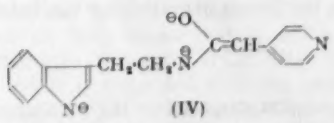

(III)

Addition of tryptamine to the doubly activated double bond of 4-1′-cyanovinylpyridine (II) would give a useful intermediate (cf. Doering and Weil, *J. Amer. Chem. Soc.*, 1947, **69**, 2461). 4-Acetylpyridine was converted quantitatively into the cyanohydrin (III; R = H) which when heated alone lost hydrogen cyanide, and was not dehydrated smoothly by thionyl chloride. The acetyl derivative (III; R = Ac) distilled at atmospheric pressure, for the most part unchanged, above 250°. The products of the pyrolysis of the benzoyl derivative (III; R = Bz) were shown to consist of benzoic acid, benzonitrile, and 4-acetylpyridine, in addition to a basic, non-ketonic fraction which was itself still a mixture. To explain this result it was postulated that, in addition to the normal alkyl–oxygen fission of esters, acyl–oxygen fission had taken place giving as primary products 4-acetylpyridine and benzoyl cyanide; the latter is known to undergo pyrolytic decomposition to benzonitrile and carbon monoxide. Ritchie (*Chem. and Ind.*, 1954, 37) independently also observed this reaction.

Alkaline hydrolysis of 4-pyridylthioacetomorpholide to 4-pyridylacetic acid hydrochloride has been described by Malan and Dean (*J. Amer. Chem. Soc.*, 1947, **69**, 1797) by a tedious procedure which in our hands failed. However, hydrolysis with hydrochloric acid gave a 70% yield. It was not possible to isolate free 4-pyridylacetic acid, even using an ion-exchange resin; this acid is formally similar to a β-keto-acid, so the zwitterion should be decarboxylated more readily than either of the ions which exist in alkaline and acid solution (cf. Doering and Pasternak, *ibid.*, 1950, **72**, 143). Although in the phosphoroazo-reaction (Goldschmit and Lautenschlager, *Annalen*, 1953, **580**, 74; cf. Part I) tryptamine and 4-pyridylacetic acid hydrochloride reacted separately in model experiments, attempts to cause them to react together failed.

In our hands ethyl 4-pyridylacetate was obtained as a stable crystalline hydrate (contrast Malan and Dean, *loc. cit.*; Lukes and Earnest, *Coll. Czech. Chem. Comm.*, 1949, **14**, 679). The methyl ester gave amides with ammonia, benzylamine, and 2-aminoethylindole. Concurrently, ethyl β-hydroxy-α-4-pyridylacrylate was prepared but did not condense smoothly with tryptamine under conditions useful for phenylformylacetic ester and other amines (Decombe, *Ann. Chim.*, 1932, **18**, 81).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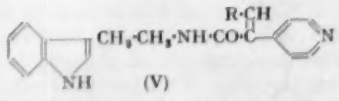

(V)

Attempts to reduce 3-(2-4′-pyridylacetamidoethyl)indole (I; X = O) to the base (I; X = H_2) with lithium aluminium hydride failed, probably owing to formation of a salt of the enolic form of the amide which is stabilised by mesomerism (as in IV). If the amide reacted with an aldehyde at the methylene group the αβ-unsaturated amide (V) obtained would be unable to lose a proton to give a similar resonating anion, and might therefore undergo reduction to the corresponding saturated or allylic amine (cf. Uffer and Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1397). Moreover this procedure would lead to the introduction of a side chain into the correct position (cf. Part I). 4-Pyridylthioacetomorpholide and litharge (not mercuric oxide) in boiling aqueous propanol gave 4-pyridylacetomorpholide in fair yield (cf. Chabrier and Renard, *Bull. Soc. chim. France*, 1949, D 272; Hofmann, *Ber.*, 1869, **2**, 455), which with benzaldehyde in acetic anhydride (cf. Philips, *J. Amer. Chem.*

Soc., 1954, **76**, 3986) gave β-phenyl-α-4-pyridylacrylomorpholide, reduced by lithium aluminium hydride to the propionomorpholide with the amide grouping intact. The selective reduction of a carbon–carbon double band in certain azlactones by lithium aluminium hydride has been reported by Baltazzi and Robinson (*Chem. and Ind.*, 1953, 868) and while the present work was in progress Snyder and Putnam (*J. Amer. Chem. Soc.*, 1954, **76**, 1893) gave another example of a reduction of unsaturated to a saturated amide. In the present case, the attachment of H^- (or an equivalent) to the β-position of the amide gives a stable mesomeric anion. In the lithium aluminium hydride reductions described, the procedure recommended by Micovic and Mihailovic (*J. Org. Chem.*, 1953, **18**, 1190) for decomposing the complex and isolating the product gave excellent results.

Attempts were now made to convert the amide (I; X = O) into the glutardialdehyde (VI), which it was considered should cyclise as indicated to a strychnine derivative (cf. Robinson and Saxton, *J.*, 1953, 2598). Panouse (*Compt. rend.*, 1951, **233**, 260, 1200) has shown that pyridinium salts are reduced by borohydride in alkaline solution to 1 : 2-dihydropyridines. The product from the methiodide of the amide (I; X = O) after this

FIG. 1. FIG. 2.

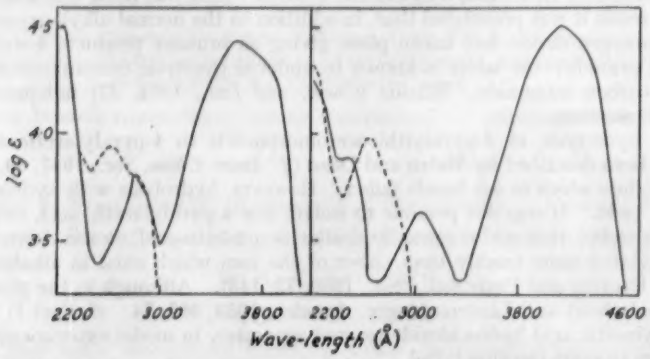
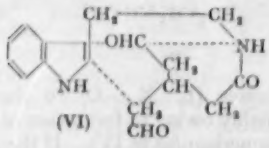


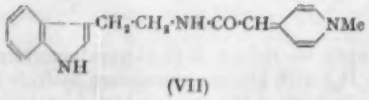
FIG. 1. *Absorption spectrum of* (– – –) *the methiodide of* (I; X = O), *in acid solution, and* (——) *the anhydro-base* (VII), *in alkaline solution.*

FIG. 2. *Absorption spectrum of the* S-*methyl derivative,* (– – –) *in acid solution* [cf. XI; R = C_4H_9O)] *and* (——) *in alkaline solution* [cf. (X)].

treatment did not appear to be the dihydropyridine. Analytical figures for hydrogen were low, and whereas 1 : 2-dihydropyridines have an absorption maximum at 3400 Å (Panouse, *Bull. Soc. chim. France*, 1953, D 53), this compound had a broad band at 3600 Å (ε 27,000) in alkaline methanol, but in acid methanol only the bands expected for the indole and



(VI)

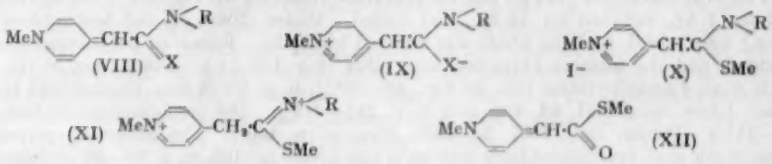


(VII)

pyridine chromophores (Fig. 1). These results were explained when the compound was shown to be reconverted by hydrogen iodide into the methiodide of (I; X = O), and to result from this methiodide by the action of alkali alone. The compound was thus the anhydro-base (VII).

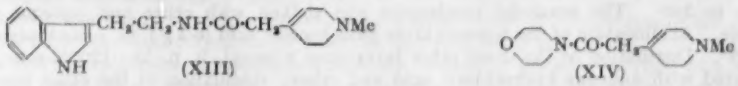
In a study of some analogous anhydro-bases, 4-pyridylthioacetopiperidide readily gave a monomethiodide, shown by a *N*-methyl determination to have the methyl group attached to the pyridine-nitrogen atom. This salt with alkali gave the anhydro-base (VIII; R = $>C_5H_{10}$, X = S), which in neutral methanol showed an intense absorption

band which disappeared on acidification. 4-Pyridylthioacetomorpholide and 4-pyridylacetomorpholide gave analogous anhydro-bases (VIII; R = C_4H_8O, X = S and O respectively). Hydrogen iodide caused reconversion into the pyridinium salts. These anhydro-bases are vinylogues of pyrid-4-one or pyrid-4-thione, and the structure (IX) must make a large contribution. No anhydro-base was isolated from the methiodide of γ-4-pyridylpropionamide where this stabilising influence would be absent.



As hydrogen iodide reacted with the anhydro-bases to give a product with the hydrogen atom on the α-carbon atom, it appeared possible that the anhydro-bases would be alkylated at this point where a side chain was needed (cf. Part I). However, the morpholino-compound (XI; R = C_4H_8O, X = S) and methyl iodide gave the methylthio-iodide (X; R = C_4H_8O). This showed an intense band at 4100 Å (ε 32,000) which disappeared in acid solution. It was a cyanine dye, with large contributions also from the structures in which the charge was associated with the other nitrogen atom or with the sulphur atom, but in acid a proton must have added to give the cation (XI; R = C_4H_8O) which showed only the absorption expected from a pyridinium ion (Fig. 2). The structure was proved by the continued action of acid which gave the expected thiol-ester (XII) (cf. Chabrier and Renard, *loc. cit.*). The thioanhydro-base (VIII; R = C_5H_{10}, X = S) also gave a cyanine dye with methyl iodide, but no crystalline product could be isolated from the two *O*-anhydro-bases.

Reduction of these two *O*-anhydro-bases failed but they were smoothly hydrogenated over palladium–strontium carbonate to the piperidyl derivatives. The indole nucleus was shown to be intact in the former product by the ultra-violet spectrum and by a positive Ehrlich test; the latter product showed no high-intensity absorption above 2200 Å. The uptake of hydrogen was steady and it did not seem promising to stop the reduction at the dihydro-stage. Panouse (*loc. cit.*) has reported that reduction of pyridinium salts in neutral or weakly acid solution with borohydride favours the formation of tetrahydro-



pyridines, and both the amides (XIII) and (XIV) were readily prepared in this way. It has recently been shown that in acid solution an αβ-unsaturated amine $R_2C{:}CR{\cdot}NR_2$ is converted into the ion $R_2CH{\cdot}CR{:}NR_2^+$ (Leonard and Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781) and it is suggested that the reduction of a pyridine to the tetrahydro-stage in solutions of low pH is due to equilibrium between the intermediate dihydropyridine (XV) and (XVI), the latter undergoing reduction to (XVII). At high pH, the cation is not formed and no reduction can take place. In an attempt to reduce the methiodide of the

amide (I; X = O) in a solution of pH just not high enough to cause precipitation of anhydro-base, the tetrahydropyridine was again obtained; even when the correct quantity of borohydride was used part of the base was reduced to the tetrahydro-stage and part left unchanged.

Experimental

In the ultraviolet spectral data, alkaline methanol was *ca.* 0·1N in potassium hydroxide; acid methanol was *ca.* 0·1N in sulphuric acid; concentration of the compound was $8 \pm 3 \times 10^{-5}$M.

4-Acetylpyridine.—Dry ethanol (69 c.c.) was dropped on to powdered sodium (27 g.) under anhydrous ether (420 c.c.), with good stirring. After 4 hours' refluxing the ether was distilled off and ethyl *iso*nicotinate (113 g.) and ethyl acetate (150 c.c.) were added. The mixture was stirred for 1 hr., refluxed for 16 hr., and cooled. Water (500 c.c.) and hydrochloric acid (300 c.c.) were added, and the whole was refluxed for 2½ hr. Excess of potassium carbonate was added, and the mixture extracted with ether (9 × 150 c.c.). Distillation of the dried extracts gave 4-acetylpyridine (74—80·5 g., 82—89%), b. p. 90°/8 mm. (Kolloff and Hunter, *J. Amer. Chem. Soc.*, 1941, **63**, 490, give b. p. 211—212°). The phenylhydrazone had m. p. 146·5—147·5° (Pinner, *Ber.*, 1901, **34**, 4250, gives m. p. 150°). The *dibromide*, prepared in benzene–acetic acid, crystallised from acetone in pale brown needles, m. p. 98—99°, resolidifying, and remelting at 205° (decomp.) (varies with the rate of heating); it liberated iodine from aqueous potassium iodide, and the active bromine content was thus estimated (Found: C, 29·9; H, 2·6; active Br, 56·8. $C_7H_7ONBr_2$ requires C, 29·9; H, 2·5; Br, 56·9%). The *methiodide* crystallised from ethanol in orange-red needles, m. p. 171—172·5° (Found: C, 36·8; H, 3·8. $C_8H_{10}ONI$ requires C, 36·5; H, 3·8%), and with silver bromide in water gave the *methobromide* which crystallised from *n*-butanol in orange prisms, m. p. 183—184° (Found: C, 43·9; H, 4·6. $C_8H_{10}ONBr$ requires C, 44·4; H, 4·6%).

4-(1-Cyano-1-hydroxyethyl)pyridine.—4-Acetylpyridine (74 g.) and anhydrous hydrogen cyanide (100 c.c.) were left at room temperature for 2 days. Much *cyanohydrin* separated, and more was obtained by evaporation (total: 91 g., 100%): it separated from benzene in prisms, the m. p. depending on the rate of heating; immersion at 85° gave m. p. 90—95° (decomp.) (Found: C, 65·0; H, 5·5. $C_8H_8ON_2$ requires C, 64·9; H, 5·4%). The *picrate* had m. p. 133—137° (decomp.) (from benzene) (Found: C, 44·9; H, 2·9. $C_{14}H_{11}O_8N_5$ requires C, 44·6; H, 2·9%). The cyanohydrin (10 g.), acetic anhydride (10 c.c.), and pyridine (20 c.c.) were kept at room temperature for 24 hr. and then distilled, to give *4-(1-acetoxy-1-cyanoethyl)pyridine*, b. p. 165—167°/14 mm., prisms, m. p. 76—78° (from benzene–light petroleum) (Found: C, 63·4; H, 5·3. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3%). The *picrate* separated from benzene in prisms, m. p. 171—174° (Found: C, 45·9; H, 3·2. $C_{16}H_{13}O_9N_5$ requires C, 45·8; H, 3·1%).

Prepared from the cyanohydrin (10 g.) and benzoyl chloride (12 c.c.) in pyridine (20 c.c.) and isolated by addition of water, *4-(1-benzoyloxy-1-cyanoethyl)pyridine* (17 g., 100%) crystallised from ethanol in needles, m. p. 112—113·5° (Found: C, 71·6; H, 4·8. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8%).

Pyrolysis of 4-(1-Benzoyloxy-1-cyanoethyl)pyridine.—This compound (40 g.) was heated in nitrogen to 350°. The semisolid condensate was shaken with ether and aqueous sodium hydroxide. Acidification of the aqueous layer gave benzoic acid (6·3 g.), m. p. and mixed m. p. 121—122°. Distillation of the dried ether layer gave a liquid, b. p. 58—120°/8 mm., which was treated with aqueous hydrochloric acid and ether; distillation of the ether layer gave benzonitrile (3·5 g.), b. p. 187—189° (Found: C, 81·4; H, 4·8. Calc. for C_7H_5N: C, 81·6; H, 4·8%), giving with hydrogen peroxide and aqueous sodium hydroxide benzamide (76%), m. p. and mixed m. p. 126·5—127·5° (Radziszewski, *Ber.*, 1885, **18**, 355). The acid layer was made strongly basic with sodium hydroxide; ether then removed a basic fraction (3·5 g.), b. p. 54—135°/9 mm., which with excess of semicarbazide hydrochloride and aqueous sodium acetate gave 4-acetylpyridine semicarbazone (0·53 g.), m. p. and mixed m. p. 216—219° (decomp.) [Emmert and Wolpert (*Ber.*, 1941, **74**, 1015) give m. p. 218—219° (decomp.)]. The mother-liquors were extracted with ether and the extracts dried (KOH, to remove acetic acid); distillation then gave a non-ketonic fraction (1 g.), b. p. 66—130°/19 mm.

4-Pyridylacetic Acid Hydrochloride.—4-Pyridylthioacetomorpholide, prepared in 85% yield by Malan and Dean's method (*loc. cit.*), gave a *hydrochloride* which separated from ethanol in prisms, m. p. 195—196·5° (Found: C, 51·2; H, 6·1. $C_{11}H_{15}ON_2ClS$ requires C, 51·1; H, 5·8%). The thiomorpholide (26·8 g.) was refluxed with hydrochloric acid (27 c.c.) for 2·5 hr., then kept at 0°. 4-Pyridylacetic acid hydrochloride (15·7 g., 70%) separated; its m. p. varied with the rate of heating; immersion at 120° gave m. p. 145—146°, unaffected by recrystallisation from ethanol (Found: C, 48·7; H, 4·7; N, 8·1. Calc. for $C_7H_8O_2NCl$: C, 48·4; H, 4·6; N, 8·1%). Malan and Dean (*loc. cit.*) give m. p. 130—131°.

Phosphoroazo-experiments.—From tryptamine and benzoic and phenylacetic acid were

prepared by the standard procedure 3-2′-benzamido- (38%), m. p. 137—138° (from benzene) (Ewins, *J.*, 1911, **99**, 273, gives m. p. 137—138°), and 3-2′-phenylacetamido-ethylindole (43%), m. p. 142—143·5°, prisms (from benzene) (Found: C, 77·3; H, 6·3. Calc. for $C_{18}H_{18}ON_2$: C, 77·7; H, 6·5%). Hahn and Ludwig (*Ber.*, 1934, **67**, 2031) give m. p. 144° for the latter.

4-Pyridylacetic acid hydrochloride was converted into the anilide (45%), m. p. 141·5—142·5° (from ethanol–water; 2 : 1) (Found: C, 73·4; H, 5·7. Calc. for $C_{13}H_{12}ON_2$: C, 73·6; H, 5·7%). Lukes and Earnest (*Coll. Czech. Chem. Comm.*, 1949, **14**, 685) give m. p. 139·5—140·5°.

Esters of 4-Pyridylacetic Acid.—The acid hydrochloride (10·7 g.) and a cold mixture of sulphuric acid (12 c.c.) and ethanol (30 c.c.) were left until dissolution was complete (2 days), then heated at 100° for 1 hr., cooled, and poured on ice and aqueous ammonia; the *ethyl ester monohydrate* separated, m. p. 41—43·5°. In a vacuum-desiccator the hydrate liquefied; on exposure to air or more quickly on addition of water, the anhydrous ester re-formed the hydrate. A sample obtained by equilibrating the anhydrous ester, after distillation, with air was analysed (Found: C, 58·9; H, 7·0. $C_9H_{11}O_2N,H_2O$ requires C, 59·0; H, 7·1%). The anhydrous ester, b. p. 122·5°/11 mm., was isolated by distillation after treatment of the hydrate with ether and magnesium sulphate. The ethyl ester picrate, separated from ethanol, had m. p. 120—121° (Malan and Dean, *loc. cit.*, give b. p. 107—108°/3 mm. for the ester, m. p. 121—123° for picrate; Lukes and Earnest, *loc. cit.*, give b. p. 119—120°/11 mm. and m. p. 121°).

The *methyl ester* (71%) was similarly prepared as an oil, b. p. 114·5°/10 mm., n^{20} 1·5084 (Found: C, 63·2; H, 6·0. $C_8H_9O_2N$ requires C, 63·6; H, 6·0%). With ammonia it gave the *amide* (70%), plates, m. p. 142—144·5° (from ethanol) (Found: C, 61·5; H, 5·8. $C_7H_8ON_2$ requires C, 61·8; H, 5·9%). Heating the methyl ester (0·5 g.) with benzylamine (3 c.c.) at 140° for 4 hr., under nitrogen, followed by removal of volatile material at 180°/11 mm. and recrystallisation from ethanol, gave needles of *4-pyridylacetylbenzylamine* (37%), m. p. 106—108° (Found: C, 74·5; H, 6·0. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%).

3-(2-4′-Pyridylacetamidoethyl)indole.—Methyl 4-pyridylacetate (0·5 g.) was heated at 150° with tryptamine (2 g.) for 4 hr. under nitrogen, then refluxed with acetic acid (4 c.c.) and acetic anhydride (4 c.c.) for 30 min., and volatile compounds were removed at 180°/11 mm. The residue was taken up in hydrochloric acid (6N; 5 c.c.), extracted four times with chloroform, made strongly alkaline with sodium hydroxide, and twice extracted with ethyl acetate. Material removed in the latter solidified; the *indole* then separated from benzene in prisms, m. p. 102—104° (Found: C, 72·9; H, 6·0; N, 15·4. $C_{17}H_{17}ON_3$ requires C, 73·1; H, 6·1; N, 15·0%). After 3 weeks the specimen had m. p. 155—157°, and separated from ethanol in needles, m. p. 160—160·5°. Subsequent preparations always gave this *polymorph* (Found: C, 73·3; H, 6·2; N, 14·9%).

Once seeds were available the following was convenient: ester (4·6 g.) and amine (5 g.) were heated at 140° for 4 hr. under nitrogen, then dissolved in ethanol, benzene was added, and the solution seeded to give the amide (5·95 g., 70%).

The amide was unaffected when refluxed with a large excess of lithium aluminium hydride in ether for 96 hr., in tetrahydrofuran for 45 hr., or in dioxan for 24 hr.

Ethyl β-Hydroxy-α-4-pyridylacrylate.—Powdered sodium (3 g.) was refluxed with ethanol (7·7 c.c.) in ether (50 c.c.) for 4 hr. Ether was then removed, and the residue refluxed with ethyl 4-pyridylacetate (10 g.) and ethyl formate (25 c.c.) for 24 hr. and poured on ice. After two ether-extractions to remove starting material, carbon dioxide precipitated the *ester* (2·25 g., 19%) which crystallised from ethyl acetate in needles; the m. p. varied with the rate of heating; immersion at 120° gave m. p. 130° (decomp.) (Found: C, 61·9; H, 5·8; N, 7·1. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·2%).

4-Pyridylacetomorpholide.—4-Pyridylthioacetomorpholide (44 g.) was refluxed with lead monoxide (150 g.) in *n*-propyl alcohol (500 c.c.) and water (140 c.c.) for 3 days. Lead compounds were removed at a centrifuge and washed with methanol. Evaporation of filtrate and washings gave the *morpholide* (24·4 g., 61%) which was obtained from benzene–light petroleum in deliquescent needles, m. p. 94—95° (Found: C, 63·7; H, 6·7. $C_{11}H_{14}O_2N_2$ requires C, 64·1; H, 6·8%). Light absorption max. at 2550 Å (ε 3500) in MeOH.

The *methiodide*, prepared in hot benzene, formed needles, m. p. 205—207° (decomp.), from ethanol (Found: C, 41·5; H, 5·0. $C_{12}H_{17}O_2N_2I$ requires C, 41·4; H, 4·9%). Light absorption max. at 2600 Å (ε 2600) in neutral MeOH, 2250, 3800 Å (ε 7800, 18,100) in alkaline MeOH. The *methotoluene-p-sulphonate* (92%) crystallised from ethanol–benzene in plates, m. p. 199—201° (decomp.) (Found: N, 7·4. $C_{19}H_{24}O_5N_2S$ requires N, 7·1%).

β-Phenyl-α-4-pyridylacrylomorpholide.—4-Pyridylacetomorpholide (4·1 g.), benzaldehyde (2·3 g.), and acetic anhydride (3·6 c.c.) were refluxed for 3½ hr., then poured into excess of aqueous

sodium hydroxide and extracted with benzene. The dried extracts were chromatographed on a short alumina column; evaporation of the eluate and recrystallisation of the residue from benzene–light petroleum gave the *acrylomorpholide* (2·62 g., 45%) which after further recrystallisation formed colourless needles, m. p. 133·5—135° (Found: C, 73·5; H, 6·3. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·1%). Light absorption max. at 2850 and 3000 Å (ε 20,000, 21,000) in neutral MeOH, 2300 and 3350 Å (ε 13,000 and 23,000) in acid MeOH. The *methiodide* separated from ethanol in pale yellow needles, m. p. 244·5—246·5° (decomp.) (Found: C, 52·4; H, 5·2. $C_{19}H_{21}O_2N_2I$ requires C, 52·3; H, 4·8%). Light absorption max. at 3400 Å (ε 10,200) in MeOH.

β-*Phenyl*-α-4-*pyridylpropionomorpholide*.—The foregoing morpholide (1 g.) was extracted (Soxhlet) into lithium aluminium hydride (0·3 g.) under ether (80 c.c.) in 1¼ hr.; the whole was then refluxed for 30 min. more and cooled, and water (0·3 c.c.), aqueous 10% sodium hydroxide (0·45 c.c.), and water (0·3 c.c.) were added successively. After filtration, evaporation gave the *propionomorpholide* (0·75 g., 74%) which after two recrystallisations from ethanol formed prisms, m. p. 135·5—137° (Found: C, 72·9; H, 6·7. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·7%). Light absorption max. at 2600 Å (ε 3100) in MeOH.

1 : 4-*Dihydro*-4-(2-3′-*indolylethylaminocarbonylmethylidene*)-1-*methylpyridine*.—3-(2-4′-Pyridylacetamidoethyl)indole gave a *methiodide* (97%) (prepared in tetrahydrofuran) which crystallised in stout needles, m. p. 178—179°, from ethanol (Found: C, 51·4; H, 4·9. $C_{18}H_{20}ON_3I$ requires C, 51·3; H, 4·8%). Light absorption max. at 2600 Å, infl. at 2800 Å (ε 8400, 6300) in neutral MeOH, 2800, 3600 Å (ε 6300, 27,000) in alkaline MeOH. It was converted by aqueous-methanolic sodium hydroxide into the *anhydro-base* (100%), which separated from anisole in pale brown needles, m. p. 191—196° (decomp.) (Found: C, 73·7; H, 6·6; N, 14·0; *N*-Me, 4·7. $C_{18}H_{19}ON_3$ requires C, 73·7; H, 6·5; N, 14·3; *N*-Me, 5·1%). {The anhydro-base was readily soluble in dilute sulphuric acid; on addition of potassium iodide, the original methiodide crystallised [m. p. and mixed m. p. 208—210° (decomp.)]}. In later work the methiodide was always obtained as a *polymorph*, fine needles, m. p. 209—210° (Found: C, 51·1; H, 4·6%).

1 : 4-*Dihydro*-1-*methyl*-4-*piperidinothiocarbonylmethylidenepyridine*.—4-Acetylpyridine (4·5 g.), piperidine (3·6 c.c.), and sulphur (1·4 g.) were refluxed for 12 hr., then poured into water, and the product was chromatographed (alumina–benzene), to give 4-*pyridylthioacetopiperidide* (2·2 g., 27%), needles (from ethanol), m. p. 94—97° (Found: C, 65·4; H, 7·5. $C_{12}H_{16}N_2S$ requires C, 65·5; H, 7·3%). Light absorption max. at 2800 Å (ε 9600) in MeOH. The *methiodide* separated from ethanol in needles, m. p. 191—194° (decomp.) (Found: C, 43·4; H, 5·4; S, 9·0; *N*-Me, 4·4. $C_{13}H_{19}N_2SI$ requires C, 43·1; H, 5·2; S, 8·8; *N*-Me, 4·2%). Light absorption max. at 2250, 2750 Å (ε 29,000, 18,000) in neutral MeOH, 2250, 3300, 4250 Å (ε 27,000, 9500, 32,000) in alkaline MeOH.

Treatment of a solution of the methiodide with alkali precipitated the *anhydro-base*, yellow needles (from ethanol), m. p. 133—136° (Found: C, 66·3; H, 7·6; S, 13·5. $C_{13}H_{16}N_2S$ requires C, 66·6; H, 7·7; S, 13·7%), reconverted by hydrogen iodide into the methiodide, m. p. and mixed m. p. 191—194° (decomp.).

Similarly 4-pyridylthioacetomorpholide gave a *methiodide*, needles, m. p. 227—230° (decomp.), from methanol (Found: C, 40·0; H, 4·8. $C_{12}H_{17}ON_2IS$ requires C, 39·6; H, 4·7%), a *methotoluene*-p-*sulphonate*, prisms, m. p. 149—153·5° (decomp.), from ethanol (Found: C, 55·6; H, 5·8. $C_{19}H_{24}O_4N_2S_2$ requires C, 55·9; H, 5·9%), and an *anhydro-base*, yellow needles (from ethanol), m. p. 197—198° (decomp.) (Found: C, 61·0; H, 6·6; S, 13·6. $C_{12}H_{14}ON_2S$ requires C, 61·0; H, 6·8; S, 13·7%), reconverted by hydrogen iodide into the methiodide, m. p. and mixed m. p. 228—231° (decomp.).

1 : 4-*Dihydro*-1-*methyl*-4-*morpholinocarbonylmethylidenepyridine*.—4-Pyridylacetomorpholide methotoluene-*p*-sulphonate (19·1 g.) was shaken with chloroform (100 c.c.) and aqueous sodium hydroxide (10%; 25 c.c.), and the aqueous layer further extracted with chloroform (3 × 50 c.c.). Solvent was removed from the dried ($MgSO_4$) extracts, and the residue taken up in benzene and filtered. Addition of light petroleum ether gave the *anhydro-base* (7·47 g., 69%) which crystallised from the mixed solvent in brown needles, changing to prisms, m. p. 123—125° (Found: C, 65·4; H, 7·2. $C_{12}H_{14}O_2N_2$ requires C, 65·5; H, 7·3%). The compound formed dichroic solutions in chloroform, green in thin layers, brown in thick. It was freely soluble in water. On storage it soon decomposed to a black tar.

β-4-Pyridylpropionamide gave a *methiodide* which separated from ethanol in prisms; the m. p. on rapid heating was 150—160°, on slow heating 163—169° probably because of polymorphism (Found: C, 36·9; H, 4·5. $C_9H_{13}ON_2I$ requires C, 37·0; H, 4·5%).

Methiodides of the Thio-anhydro-bases.—Treatment of the thiomorpholide anhydro-base with

methyl iodide in tetrahydrofuran gave **1-*methyl*-4-(2-*methylthio*-2-*morpholinovinyl*)*pyridinium iodide***, which separated from ethanol–tetrahydrofuran (1 : 1) in yellow needles, m. p. 195—198° (decomp.) (Found : C, 41·6; H, 5·1; *N*-Me, 3·4; *C*-Me, 0·0. $C_{13}H_{19}ON_2SI$ requires C, 41·3; H, 5·0; 1*N*-Me, 4·0%). Light absorption max. at 2500, 3050, and 4100 Å (ε 7700, 4200, and 32,000) in neutral MeOH, 2650 Å (ε 9500) in acid MeOH.

This iodide (1 g.) was heated at 100° for 8 min. with 2N-sulphuric acid (10 c.c.), then cooled and treated with 2·5N-sodium hydroxide (15 c.c.), affording **1 : 4-*dihydro*-1-*methyl*-4-(S-*methylthiocarbonylmethylene*)*pyridine*** (0·35 g., 73%) which separated from ethanol in pale yellow prisms, m. p. 134·5—136·5° (Found : C, 59·9; 59·4; H, 6·1, 6·0; N, 7·9. $C_9H_{11}ONS$ requires C, 59·7; H, 6·1; N, 7·7%). Light absorption max. at 2300, 2600, 4100 (ε 5500, 2000, 21,600) in neutral MeOH, 2300, 2600 Å (ε 7000, 5000) in acid MeOH.

The thiopiperidide anhydro-base similarly gave **1-*methyl*-4-(2-*methylthio*-2-*piperidinovinyl*)-*pyridinium iodide***, which separated from methanol in yellow needles, m. p. 177—180° (Found : C, 44·5; H, 5·3. $C_{14}H_{21}N_2SI$ requires C, 44·7; H, 5·6%).

1-*Methyl*-4-*piperidylacetomorpholide*.—**1 : 4**-Dihydro-1-methyl-4-morpholinocarbonylmethylidenepyridine (1·5 g.) in ethanol (40 c.c.) was shaken with 1% palladium–strontium carbonate (7 g.) under hydrogen at normal pressure. Approx. 3 mols. of hydrogen were absorbed. The mixture was filtered, solvent removed from the filtrate, and the residue crystallised from light petroleum to give the ***morpholide*** (1·08 g., 70%) in deliquescent fronds, m. p. 65—67·5° (Found : C, 63·4; H, 9·8. $C_{13}H_{22}O_2N_2$ requires C, 63·7; H, 9·7%), which showed only end absorption above 2200 Å. The ***methotoluene*-p-*suphonate***, prepared in benzene, separated from ethanol in stout plates, m. p. 242—243° (Found : N, 7·0. $C_{20}H_{28}O_5N_2S$ requires N, 7·0%).

3-[2′-(1″-*Methyl*-4″-*piperidylacetamido*)*ethyl*]*indole*.—A suspension of **1 : 4**-dihydro-4-(2-3′-indolylethylaminocarbonylmethylidene)-1-methylpyridine (2 g.) in ethanol (60 c.c.) was shaken with 1% palladium–strontium carbonate (4 g.) under hydrogen. After 24 hr., filtration and evaporation gave the ***piperidine*** derivative (1·83 g., 81%) which separated from ethanol in prisms, m. p. 181—182° (Found : C, 71·9; H, 8·4. $C_{18}H_{25}ON_3$ requires C, 72·2; H, 8·4%). Light absorption max. at 2800 Å (ε 7300) in MeOH. With warm Ehrlich's reagent a bright magneta colour appeared.

1 : 2 : 3 : 6-*Tetrahydro*-1-*methyl*-4-*pyridylacetomorpholide Methiodide*.—Potassium borohydride (0·3 g.) was added, all at once, to 4-pyridylacetomorpholide methotoluene-*p*-sulphonate (1 g.) in water (2 c.c.). The mixture became hot and effervesced vigorously. After 1 hr., the whole was extracted with chloroform (2 × 6 c.c.). The dried extracts were evaporated to an oil, which was taken up in benzene. When methyl iodide was added the ***methiodide*** (0·5 g., 54%) separated; recrystallised twice from ethanol, it formed prisms, m. p. 179—180° (Found : C, 42·2; H, 6·3; N, 7·6. $C_{13}H_{23}O_2N_2I$ requires C, 42·6; H, 6·3; N, 7·6%).

3-[2′-(1″ : 2″ : 3″ : 6″-*Tetrahydro*-1″-*methyl*-4″-*pyridylacetamido*)*ethyl*]*indole*.—**1 : 4**-Dihydro-4-(2-3′-indolylethylaminocarbonylmethylidene)-1-methylindole (1 g.) was dissolved in 2N-acetic acid (3 c.c.), and 2N-sodium carbonate (10 c.c.) added, followed by potassium borohydride (0·2 g.). There was a slight gas evolution, and solid began to separate. After 5 min., the ***product*** (0·82 g., 81%) was filtered off and twice recrystallised from ethanol, to give plates or needles, m. p. 216—217° (Found : C, 72·5; H, 7·8. $C_{18}H_{23}ON_3$ requires C, 72·7; H, 7·7%). Light absorption max. at 2800 Å (ε 4800) in MeOH.

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Chemical Action of Ionising Radiations in Solution. Part XIV. The Action of X-Rays (200 kv) on Some Aliphatic Amines in Aqueous Solution with Particular Reference to the Formation of Oximes.*

By G. G. Jayson, G. Scholes, and J. Weiss.

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Oximes are produced by irradiation with *X*-rays (200 kv) of primary and secondary aliphatic amines in alkaline solutions provided that molecular oxygen is present. Quantitative studies have been carried out with ethylamine and diethylamine, and the effects of pH and other factors examined. The process involves radical attack at the free (uncharged) amino-group. Some light has been thrown on the mechanism of this reaction by the observation that, in addition to oximes, nitroparaffins are produced in the irradiation of the primary aliphatic amines; it is suggested that organic peroxy-radicals act as intermediates.

In a preliminary publication (Scholes and Weiss, *Nature*, 1951, **167**, 693) it was reported that hydroxylamine was detected in the aqueous solutions of the following amino-compounds which had been irradiated with *X*-rays (200 kv): amino-acids (*e.g.*, alanine, lysine), amino-purines (*e.g.*, adenine), and amines (*e.g.*, ethylamine, propylamine, histamine). In a large number of the systems, however, particularly at pH ~7, the yields of hydroxylamine were quite small. On the other hand, more significant quantities could be detected on irradiation of alkaline solutions of the primary aliphatic amines which, therefore, appeared suitable for further studies of the nature of this process.

In general, chemical transformations induced by ionising radiations in dilute aqueous systems are due, in the first instance, to the production of free radicals from the water, according to the net process (Weiss, *Nature*, 1944, **153**, 748; *Brit. J. Radiol.*, 1947, Suppl. **1**, 56):

$$H_2O \longrightarrow H + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In the presence of dissolved molecular oxygen this can be followed by the reaction

$$H + O_2 \longrightarrow HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The radicals thus formed may then react with the solutes. Recently it has been shown that, in addition to reaction (1), decomposition of water takes place with the production of molecular hydrogen and hydrogen peroxide (Allen, *Ann. Rev. Phys. Chem.*, 1952, **3**, 57), *viz.*,

$$2H_2O \longrightarrow H_2 + H_2O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

With hard *X*-rays, the extent of reaction (3) is small compared to that of reaction (1), but must, nevertheless, be considered in any quantitative studies of the action of these radiations.

Preliminary Experiments.—In confirmation of previous observations, hydroxylamine could be readily detected in irradiated alkaline solutions of several primary aliphatic amines by Endres and Kaufman's method (*Annalen*, 1937, **530**, 184), involving oxidation to nitrite by iodine at room temperature, a process which is normally complete within about 15 minutes, the nitrite thus formed being estimated by the Griess–Ilosvay reagent.

Aerated solutions of the amines (0·1M) at pH ~11 were irradiated with 200 kv *X*-rays, total doses varying between 2 and 6×10^{-6} ev/*N* per ml. being used. However, oxidation was incomplete after 15 min. at room temperature, additional quantities of nitrite being slowly produced. Further, the corresponding aldehydes could be isolated from the irradiated solutions as their 2 : 4-dinitrophenylhydrazones. These observations suggested that oximes and not necessarily free hydroxylamine were present after irradiation. Total hydroxylamine content was, therefore, determined by the "hot oxidation" procedure for oximes as first suggested by Endres (*Annalen*, 1935, **518**, 109).

* Part XIII, *J.*, 1954, 3248.

Table 1 shows some results obtained by irradiating methyl-, ethyl-, and propyl-amine. It can be seen that additional amounts of nitrite are produced by the iodine oxidation at higher temperatures; this is characteristic of solutions containing oximes (*e.g.*, formaldoxime) but unlike those of pure hydroxylamine.

Because of the equilibrium between aldehyde, hydroxylamine, and oxime in aqueous systems, it is not possible on the basis of these experiments alone to decide whether oxime or hydroxylamine is the primary product of irradiation; this question is discussed more fully below. The yields of free nitrite in the irradiated solutions (cf. Table 1) were determined by direct addition of the Griess–Ilosvay reagent. However, nitrite was present only in solutions which had received relatively high doses.

TABLE 1. *Irradiation of aqueous solutions of some primary aliphatic amines with* X*-rays* (200 kv). *Comparison of yields of nitrite by " cold " and " hot " oxidation with iodine.*

Solution	Dose [10^{-6} (ev/*N*) per ml.]	Free nitrite (10^{-6} mole per ml.)	Nitrite after cold oxidation (10^{-6} mole/ml.)	Nitrite after hot oxidation (10^{-6} mole/ml.)
NH_2Me, 0·09M; pH 12·1...	2·08	0·00	0·91	1·27
	2·59	0·08	1·29	1·73
NH_2Et, 0·13M; pH 10·3...	1·73	0·00	0·52	1·00
	3·46	0·10	1·10	2·00
NH_2Pr^n, 0·10M; pH 12·0	6·06	0·50	1·30	1·60
Hydroxylamine	—	—	1·95	1·90
Acetaldoxime	—	—	1·08	1·81

The possibility that *N*-substituted hydroxylamines were formed by irradiation and then oxidised to nitrite by the above method was examined in tests with *N*-methylhydroxylamine solutions. With a solution containing $2{\cdot}5 \times 10^{-7}$ mole/ml. (*i.e.*, of the order of the concentrations which may be expected to be produced in the irradiated solutions) no nitrite was formed on oxidation by iodine at room temperature, and the " hot oxidation " procedure converted only about 1% of the *N*-methylhydroxylamine into nitrite. Hence it was concluded that the nitrite-forming substances present in the irradiated solutions were oximes. These observations do not, of course, exclude the possibility that substituted hydroxylamines are also formed.

Further light was thrown on the mechanism by the observation that the corresponding nitroparaffins were also produced in the irradiation of primary amines in aqueous solutions containing oxygen. This has been investigated particularly in the case of ethylamine; the nitroethane formed was detected by Türber and Uhlin's method (*Angew. Chem.*, 1949, **61**, 74). Analytically, the method is not particularly suitable for this system, there being some interference in colour development. However, by blank tests (see Experimental) estimates of the yields have been obtained from which it would appear that the amounts of nitroparaffin formed are roughly equivalent to those of the oxime.

Irradiations of alkaline solutions of diethylamine and triethylamine were carried out in a similar manner. In the case of the secondary amine, oxime (acetaldoxime) was again present after irradiation. However, only aldehyde (acetaldehyde) could be detected in the irradiated tertiary amine solutions. Thus, oxime formation can occur only if the amine nitrogen carries a hydrogen atom.

Since all these experiments were in the presence of molecular oxygen, the formation of hydrogen peroxide was expected and was detected by means of the titanium sulphate reagent. In each instance, the formation of ammonia was established by Nessler's reagent.

When, however, the primary and secondary amine solutions were irradiated in the absence of dissolved molecular oxygen, no oxime (or nitroparaffin) could be detected. It seemed evident therefore, that oxygen plays an important part in the mechanism of these processes.

Quantitative Experiments.—Ethyl-, diethyl-, and triethyl-amine were selected as representative of the primary, secondary, and tertiary aliphatic amines. Total hydroxylamine (oxime) was determined by the " hot iodine oxidation " method, hydrogen peroxide with titanium sulphate, and acetaldehyde as its 2 : 4-dinitrophenylhydrazone. (This method was shown to determine total aldehyde content, *i.e.*, including that available in the form of oxime).

(a) *Ethylamine.* Fig. 1 shows some typical yield–dose plots obtained from the irradiation of an aqueous ethylamine solution (0·068M; pH = 10·75). Experiments were carried out with oxygen-saturated and with air-equilibrated solutions. The initial yields were identical under both these conditions, that of total hydroxylamine (oxime) corresponding to a G-value (molecules/100 ev of energy absorption) of ~0·6, and that of total measurable aldehyde of G ~1·4. Small quantities of nitrite were also detected but only after relatively high doses had been applied to the solutions (cf. Fig. 1) and, therefore, they appear to be the result of secondary oxidation of the primary products of irradiation.

FIG. 1. *Irradiation of aqueous solutions of ethylamine* (0·068M, pH = 10·75) *with X-rays* (200 kv). (Temp. 20°.)

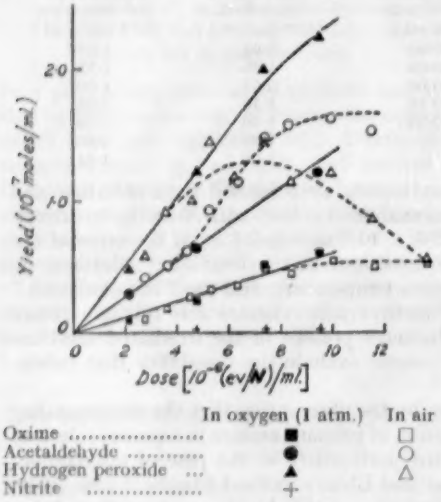
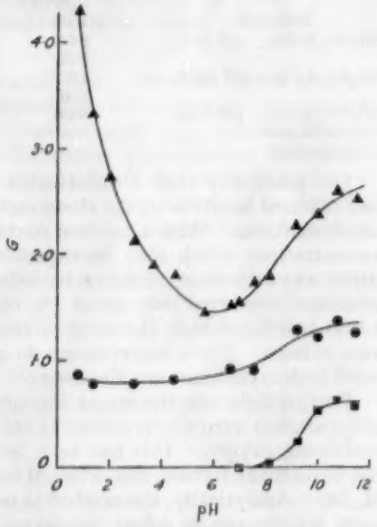


FIG. 2. pH-*Dependence of the initial yields of oxime* (■), *acetaldehyde* (●), *and hydrogen peroxide* (▲) *in irradiation of aqueous solutions of ethylamine* (0·068M) *with X-rays* (200 kv) *in the presence of oxygen* (1 *atm.*). (Temp. 20°.)



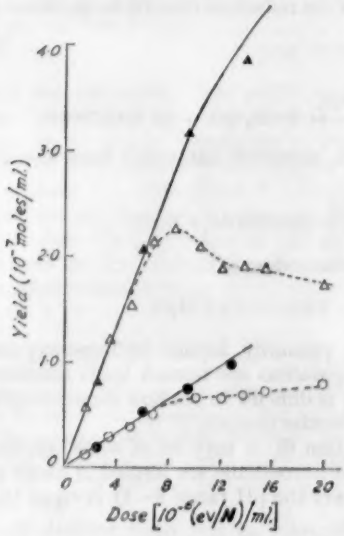
The pH-dependence of the initial yields in oxygen-saturated solutions was obtained from such yield–dose plots, as shown in Fig. 2. The initial yields of all the measured products vary with pH; oxime formation occurs only in alkaline solutions and increases with increasing alkalinity at pH> ~8, giving eventually a yield of G ~0·6 at pH ~11; the yields of acetaldehyde also increase over the same pH range, and it is noteworthy that this increase is of the same order as that of oxime. Since dissociation of the ethylamine cation takes place in this range according to $Et{\cdot}NH_3^+ \rightleftharpoons Et{\cdot}NH_2 + H^+$, these observations suggest that oxime can only result from radical attack on the free uncharged amino-group.

In solutions saturated with air (Fig. 1) oxime formation more or less ceases after a total dose of the order of $7{\cdot}5 \times 10^{-6}$ ev/N per ml. Secondary decomposition of hydrogen peroxide and an enhanced formation of aldehyde begin even before this dose is reached. These effects can be attributed to the utilisation and eventual exhaustion of the dissolved molecular oxygen. At least one-third (Fig. 1) of the available oxygen is not converted into measurable hydrogen peroxide. If no peroxide decomposition had occurred before the "break point" (at ~$7{\cdot}5 \times 10^{-6}$ ev/N per ml.) the maximum yield expected after this dose would have been 2×10^{-7} mole/ml., *i.e.*, corresponding to that in solutions saturated with oxygen; included in this value is the hydrogen peroxide produced by reaction (3), which, up to this point amounts to $0{\cdot}38 \times 10^{-7}$ mole/ml. ($G = 0{\cdot}50$). Thus the peroxide

formed by radical processes is $1{\cdot}62 \times 10^{-7}$ mole/ml. Under these conditions the total available oxygen present in the solutions saturated with air was $\sim 2{\cdot}9 \times 10^{-7}$ mole/ml. (at 20°). Therefore, $\sim 1{\cdot}3 \times 10^{-7}$ mole/ml. of oxygen (corresponding to $G \sim 1{\cdot}7$) have entered into reactions involving the solute molecules and are eventually incorporated in the final products. That these reactions are essentially those leading to oxime is suggested by the fact that " oxygen loss " in acid solution, where no oxime is formed, is much less ($G \sim 0{\cdot}5$, Fig. 3).

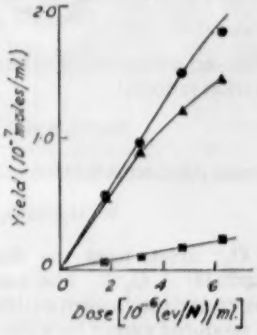
(b) *Diethylamine and triethylamine.* Fig. 4 gives the yield–dose plots obtained from the irradiation of an alkaline solution of diethylamine in which the concentration of the

FIG. 3. *Irradiation of aqueous solution of ethylamine* (0·068M, pH = 1·35) *with X-rays* (200 kv). (Temp. 25°.)



	In oxygen (1 atm.)	In air
Acetaldehyde	●	○
Hydrogen peroxide ...	▲	△

FIG. 4. *Irradiation of aqueous solutions of diethylamine* (0·0655M, pH = 11·2) *with X-rays* (200 kv) *in the presence of oxygen* (1 *atm.*). (Temp. 20°.)



■ Oxime
● Acetaldehyde
▲ Hydrogen peroxide.

secondary amino-group was identical with that of the free primary amino-group in the above ethylamine solutions. Table 2, in addition, summarises some G values obtained from di- and tri-ethylamine solutions irradiated at different pH values. The yields of aldehyde from these compounds in alkaline solution were much greater than those obtained

TABLE 2. *Irradiation of aqueous solutions of di- and tri-ethylamine with X-rays* (200 kv) *at different* pH.

		Yield (G)		
Solution	pH	Hydrogen peroxide	Acetaldehyde	Oxime
$NHEt_2$ (0·065M)	11·16	3·16	3·16	0·36
	2·82	2·58	0·77	0·00
NEt_3 (0·059M)	11·95	2·95	3·20	0·00
	2·35	2·70	0·76	0·00

from ethylamine at similar pH's; in acid solution, however, all three amines yielded about the same amount of aldehyde ($G = 0{\cdot}7$—$0{\cdot}8$).

It seems, therefore, that three conditions are necessary for the production of oximes when aqueous amine solutions are subjected to ionising radiations: (i) The presence of

a hydrogen atom on the nitrogen of the amino-group. (ii) The primary or secondary amino-group must be present in the free (uncharged) state. (iii) Molecular oxygen must be present in solution. These conditions are closely similar to those required for the production of nitrite by irradiation of ammonium salt solutions (Rigg, Scholes, and Weiss, *J.*, 1952, 3034), where the presence of molecular oxygen was essential, and the yield was dependent on the concentration of free ammonia molecules. The mechanism then proposed for ammonia oxidation involved the following initial steps:

$$NH_3 + OH \longrightarrow NH_2 + OH_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4a)$$

$$NH_2 + O_2 \longrightarrow NH_2{\cdot}O_2{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4b)$$

Nitrite can then readily result from further oxidation of the $NH_2{\cdot}O_2{\cdot}$ radical. In the case of a primary amine the organic peroxy-radical ($R{\cdot}CH_2{\cdot}NH{\cdot}O_2{\cdot}$) produced in an identical fashion could on oxidation lead to a nitroparaffin, or, on reduction directly to an oxime, *i.e.*:

$$R{\cdot}CH_2{\cdot}NH{\cdot}O_2{\cdot} \xrightarrow{(\text{oxidn.})} R{\cdot}CH_2{\cdot}NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5a)$$

$$R{\cdot}CH_2{\cdot}NH{\cdot}O_2{\cdot} \xrightarrow{(\text{redn.})} R{\cdot}CH_2{\cdot}NH{\cdot}O_2H \xrightarrow{(-H_2O)} R{\cdot}CH_2{\cdot}NO \longrightarrow R{\cdot}CH{:}N{\cdot}OH \quad . \quad (5b)$$

Simultaneous formation of oxime and nitroparaffin, moreover, can result from the simple dismutation process:

$$2R{\cdot}CH_2{\cdot}NH{\cdot}O_2{\cdot} \longrightarrow R{\cdot}CH_2{\cdot}NO_2 + R{\cdot}CH{:}N{\cdot}OH(+ H_2O) \quad . \quad . \quad . \quad . \quad . \quad (6)$$

In alkaline solution reduction may also take place according to

$$R{\cdot}CH_2{\cdot}NH{\cdot}O_2{\cdot} + O_2^- \longrightarrow O_2 + R{\cdot}CH{:}N{\cdot}OH(+ H_2O) \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where O_2^- arises from the dissociation of any primarily formed hydroperoxy-radical ($HO_2 \rightleftharpoons H^+ + O_2^-$). The mere fact that nitroparaffins are formed lends considerable support to the mechanism outlined above, since it is difficult to see how these compounds can be produced except by a process involving molecular oxygen.

With regard to the dismutation process (reaction 6), it may be of some significance that in the case of ethylamine, at least, oxime and nitroethane are formed in about equal amounts, and also that the increase in aldehyde over the pH range 8—11 is equal to that of oxime over this region (Fig. 2).

However, dismutation according to the scheme

$$2R{\cdot}CH_2{\cdot}NH{\cdot}O_2{\cdot} \longrightarrow 2R{\cdot}CH_2{\cdot}NH{\cdot}O{\cdot} + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8a)$$

$$2R{\cdot}CH_2{\cdot}NH{\cdot}O{\cdot} \longrightarrow R{\cdot}CH{:}N{\cdot}OH + R{\cdot}CH_2{\cdot}NH{\cdot}OH \quad . \quad . \quad . \quad . \quad (8b)$$

i.e., oxime production accompanied by formation of a substituted hydroxylamine, cannot be entirely ruled out, since it is not known whether the latter substance is produced. Nitroparaffin could then only arise from an oxidation involving a hydroxyl (or HO_2) radical, *viz.*,

$$R'{\cdot}NH{\cdot}O_2{\cdot} + OH \longrightarrow R'{\cdot}NO_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9a)$$

$$R'{\cdot}NH{\cdot}O_2{\cdot} + HO_2 \longrightarrow R'{\cdot}NO_2 + H_2O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9b)$$

The almost constant yield of aldehyde at pH <8 is presumably the result of dehydrogenation of the amine at the α-carbon atom, and there is no reason to believe that such an attack does not also take place in alkaline solution. Indeed, the excess of aldehyde over total oxime and also the formation of ammonia in alkaline solutions suggest the occurrence of such processes.

With secondary amines, *e.g.*, diethylamine, oxime formation is linearly dependent upon dose (Fig. 4); the compound must therefore be a primary product of the irradiation. On a basis similar to that outlined above, one would expect oxime production to involve, as intermediates, peroxy-radicals of the structure $R''_2{\cdot}NO_2{\cdot}$. The higher yields of aldehyde

from the secondary and tertiary amines are not unexpected, since radical attack at the nitrogen atom can presumably lead to oxidation of more than one alkyl group.

The yields of *total* hydroxylamine produced on irradiation of some amino-compounds of biological importance are shown in Table 3; in these experiments the " hot oxidation "

TABLE 3. *" Total hydroxylamine " by irradiation with* X*-rays* (200 kv) *of aqueous solutions of organic amino-compounds of biological interest.*

Solution irradiated		Yield of " total hydroxylamine "	
Dose = $5{\cdot}4 \times 10^{-6}$ ev/N per ml.	pH	10^{-6} moles/ml.	G
L-Lysine ($2{\cdot}3 \times 10^{-3}$M)	11·0	0·61	0·11
D-Arginine ($2{\cdot}3 \times 10^{-3}$M)	11·5	0·63	0·12
Histamine ($2{\cdot}7 \times 10^{-3}$M)	10·3	0·41	0·08
Albumin * (0·075%)	10·8	0·22	0·03
Glycine (0·028M)	12·1	2·79	0·51
Glycylglycine (0·028M)	11·85	1·96	0·36
Diglycylglycine (0·028M)	11·90	1·11	0·20

* Dose = $9{\cdot}2 \times 10^{-6}$ ev/N per ml.

method was employed. The yields were in all cases higher than those which had been obtained previously by using the cold oxidation procedure (Scholes and Weiss, *loc. cit.*; Scholes, Ph.D. Thesis, University of Durham, 1952) and also indicate the production of oximes. Concentrations of the order of 10^{-5}M (total) hydroxylamine can be produced by doses of about 5×10^4 r (Table 3). It is known that hydroxylamine is a strong cell poison and enzyme inhibitor (cf. Kaplan, *J. Biol. Chem.*, 1954, **211**, 419); it is not impossible therefore that the production of this substance from amino-compounds may be of some significance in the biological action of ionising radiations; this may be particularly accentuated in local regions of relatively high pH.

EXPERIMENTAL.

Irradiations.—The amine solutions (200 ml.) were irradiated with *X*-rays generated from a Victor Maximar set, operating at 200 kv and 15 ma, the irradiation arrangements being essentially those employed by Farmer, Stein, and Weiss (*J.*, 1949, 3241). The dose rate was determined by measuring the oxidation of 10^{-3}M-ferrous sulphate in 0·1N-sulphuric acid and was $1{\cdot}72 \times 10^{-7}$ ev/N per ml. per min., $G_{(Fe^{3+})}$ being taken as 15·5 (Farmer, Rigg, and Weiss, *J.*, 1955, 582).

Triply distilled water was used for all irradiation experiments, obtained by redistilling ordinary distilled water from alkaline potassium permanganate and then from dilute orthophosphoric acid. " AnalaR " sulphuric acid was used when pH's other than the natural alkaline pH's of the amine solutions were required.

All amines were purified before irradiation *via* their hydrochlorides, the free amines being then regenerated by distillation from alkali into triply distilled water.

Irradiations were carried out with air-equilibrated, oxygen-saturated, and evacuated solutions. Saturation with oxygen was effected by passing the gas through the solutions for approximately 15 min. For evacuation, first a Hyvac oil pump and finally a mercury-diffusion pump were employed. To avoid losses of amine it was necessary to evacuate, in the first instance, acidic solutions (in sulphuric acid), which were then made alkaline by tipping into the solution the required amounts of sodium hydroxide stored in a side arm of the radiation vessel.

The pH's of the solutions were checked after irradiation.

Detection and Determination of the Irradiation Products.—Ammonia. Owing to interference from the amines it was only possible to carry out qualitative tests. An exact amount of Nessler's reagent was added to 5 ml. of irradiated solution and also to 5 ml. of the blank. Both gave a precipitate (due to the amine), but the yellower colour of the irradiated samples was quite distinct in all the cases examined.

Nitroethane. This was detected by the red-brown coloration on addition of diazotized sulphanilic acid (Türber and Uhlin, *loc. cit.*). The relative quantities of reagents given by these authors were adhered to; the volumes, however, were increased so as to allow measurement on a " Spekker " photoelectric absorptiometer, a 4-cm. cell and a blue-green filter (Ilford 603) being used. Although the amine present gave a yellow-green colour with the reagents, it was

possible in test solutions to detect quantities down to 10^{-6}M. From a quantitative point of view, difficulty was encountered owing to interference from other irradiation products. However, estimates of the yields could be obtained by comparison with standard nitroethane solutions, containing ethylamine and also the other known radiation products, in such quantities as to simulate the irradiated solutions.

Hydrogen peroxide. This was determined by means of titanium sulphate (Eisenberg, *Ind. Eng. Chem. Anal.*, **1943**, **15**, 327). Aliquot parts were slightly acidified, treated with 5 ml. of titanium reagent, and then made up to 50 ml. The extinctions were measured on the "Spekker" instrument by use of an Ilford 601 (blue-violet) filter.

Oxime, hydroxylamine, and nitrite. The methods described by Endres and Kaufman (*loc. cit.*) were used for these compounds.

To determine nitrite, 10-ml. aliquot parts were treated with 2 ml. of sulphanilic acid solution (5·25 g. in 100 ml. of 20% v/v acetic acid) and 2 ml. of α-naphthylamine reagent (0·6 g. in 100 ml. of 5% acetic acid). The mixture was set aside for 15 min. It was then diluted to 50 ml., and the extinction measured by means of a large (4 cm.) cell and a green (Ilford 604) filter. Hydroxylamine was determined as nitrite after oxidation with iodine. To 10-ml. aliquot portions, 2 ml. of sulphanilic acid solution and 0·2 ml. of iodine reagent (0·6 g. in 100 ml. of glacial acetic acid) were added. After 15 min. at room temperature, the excess of iodine was removed with a few drops of aqueous sodium thiosulphate (2% w/v), and the solution immediately treated with α-naphthylamine reagent as above.

Oxime was also determined as nitrite: 0·2 ml. of iodine reagent was added to 10 ml. of the aliquot portion. The solution was brought quickly to the boil and cooled at once in running water; 2 ml. of sulphanilic acid and a further 0·1 ml. of iodine reagent were added. The analysis was then continued as described above for hydroxylamine. This method was accurate to within ±5%, there being invariably some very slight losses owing to further oxidation of nitrite to nitrate.

The α-naphthylamine reagent is somewhat unstable and was only used when controls gave very low extinctions.

Aldehydes. These were identified as their 2 : 4-dinitrophenylhydrazones. 100 ml. of irradiated amine solution were acidified and subsequently treated with 50 ml. of 2 : 4-dinitrophenylhydrazine (0·25% w/v in 30% perchloric acid). The mixture was set aside for ½ hr., then extracted with carbon tetrachloride. The solvent was removed by vacuum-distillation, and the residue chromatographed on paper by using a light petroleum–methanol solvent (Meigh, *Nature*, **1952**, **170**, 579).

The quantitative determination of acetaldehyde in irradiated amine solutions was carried out by Johnson and Scholes's method (*Analyst*, **1954**, **79**, 217): 10 ml. of sample were slightly acidified with sulphuric acid, 5 ml. of the 2 : 4-dinitrophenylhydrazine reagent were added, and the mixture set aside for 15 min. It was then extracted for 2-min. and for ½-min. periods with 20 ml. and 5 ml. of carbon tetrachloride, respectively. The extract was diluted with ethanol, 2 ml. of 0·1N-ethanolic sodium hydroxide were added, and after thorough mixing the solution was made up to 50 ml. with ethanol. Extinctions were measured in a 4-cm. cell with a blue-green (Ilford 603) filter. By this method the total amount of acetaldehyde, including that combined as oxime, in solution was measured.

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KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, February 18th*, 1955.]

The Base-catalysed Hydrolysis of Certain Aliphatic Amides and p-*Alkylbenzamides.*

By J. Packer, A. L. Thomson, and J. Vaughan.

[Reprint Order No. 6185.]

The aqueous alkaline hydrolysis of acetamide, propionamide, *iso*-butyramide, and trimethylacetamide has been followed at 50° and 70° over a range of concentrations of sodium hydroxide. The order of reactivity appears to be governed by the inductive effects of the alkyl groups. Hydrolysis of benzamide, *p*-toluamide, *p*-ethylbenzamide, *p-iso*propylbenzamide, and *p-tert.*-butylbenzamide under similar conditions has also been examined. Within the limits of experimental error, the rates of hydrolysis of these *p*-alkylbenzamides are the same.

Kinetic studies (Reid, *Amer. Chem. J.*, 1899, **21**, 284; 1900, **24**, 397) indicate that the alkaline hydrolysis of a simple amide follows the mechanistic type summarised by Ingold as $B_{AC}2$. Electron-attracting substituents accelerate, and electron-donating substituents retard the reaction. Thus any *C*-alkylated acetamide would be expected to hydrolyse more slowly than the parent compound, even if steric retardation were absent. In the series, acetamide, propionamide, *iso*butyramide, and trimethylacetamide, the order of reactivity would depend on the relative contributions of the inductive and hyperconjugative effects, although related data (*e.g.*, alkaline hydrolysis of the corresponding ethyl esters; Davies and Evans, *J.*, 1940, **339**; Evans, Gordon, and Watson, *J.*, 1938, **1438**) suggest that in the simple aliphatic amides the order would probably be dictated by the inductive effect. A kinetic study has now been made, at 50° and 70°, of the hydrolysis with sodium hydroxide in aqueous solution. Because similar hydrolysis of *p*-alkylbenzamides should be relatively free from primary steric effects and should also provide more favourable conditions for hyperconjugation, the series, *p*-toluamide, *p*-ethylbenzamide, *p-iso*propylbenzamide and *p-tert.*-butylbenzamide, was also examined.

Experimental and Results

Amides.—Of the purified materials acetamide had m. p. 81°, propionamide 81°, and *iso*-butyramide (prepared by Kent and McElvain's method; *Org. Synth.*, 1945, **25**, 58) 128°. Trimethylacetamide was prepared from the purified acid by Kent and McElvain's method. Repeated recrystallisations from ethyl acetate and from ether gave a sample melting at 157° (cf. m. p. 153—154°, Franchimont and Klobbie, *Rec. Trav. chim.*, 1887, **6**, 238; 155—156°, Haller and Barrer, *Compt. rend.*, 1909, **148**, 129). Benzamide melted at 129°, toluamide at 162°, unchanged after many recrystallisations (Beilstein records several values between 156° and 165°), and *iso*propylbenzamide (prepared from the corresponding acid by Berliner's procedure, *J. Amer. Chem. Soc.*, 1952, **74**, 4940) at 153°. *p-tert.*-Butylbenzamide, prepared from *p*-bromo-*tert.*-butylbenzene *via* the Grignard compound and the acid resulting from carboxylation, melted at 173° (cf. 171°; Kelbe and Pfeiffer, *Ber.*, 1886, **19**, 1726). Gattermann and Rossolymo (*Ber.*, 1890, **23**, 1195) recorded m. p. 115—116° for *p*-ethylbenzamide; our sample was obtained by a procedure similar to that used for the *tert.*-butyl compound and melted at 166°, although the acid had the accepted m. p., 114°. Gattermann and Rossolymo's preparation was therefore repeated; the resulting amide, after two recrystallisations from water, had m. p. 162°, and a mixed m. p. determination with our original preparation confirmed identity of the two samples (Found: C, 72·5; H, 7·35; N, 9·45. Calc. for $C_9H_{11}ON$: C, 72·5; H, 7·4; N, 9·4%).

Hydrolyses.—The bath temperatures were maintained to within 0·05° for all runs. For each run, a set of ten tubes (see Figure) was used. The reaction mixture was contained in the tube and in the bulb were placed 10 ml. of a sulphuric acid solution sufficiently concentrated to ensure slight residual acidity on mixing with the hydrolysate. Tubes were removed from the bath at appropriate intervals for analysis and placed in ice–salt to arrest hydrolysis, the tap being opened at the same time to effect mixing. After this neutralisation of the hydrolysate, the method for ammonia determination depended on whether or not the amide concerned interfered with the direct titration method (*J.*, 1952, 3264).

Aliphatic Amides.—There was no measurable reaction of acetamide or propionamide with hypobromite under the experimental conditions; *iso*butyramide reacted very slightly but the extent was insufficient to render uncertain the titration for ammonia. In each of these cases, therefore, ammonia determination was carried out in the presence of the amide. Trimethylacetamide reacted extensively with hypobromite; the distillation procedure was therefore followed and proved free from complications. The molar ratio of alkali to amide was >100 : 1 in every run and the kinetics were of first order with respect to amide. For each amide, variation of amide concentration confirmed pseudo-unimolecularity and runs with sodium chloride additions indicated a freedom from salt effect. The range of sodium hydroxide concentration was 0·03125—0·75M, and at least two runs were carried out at each of the concentrations, with the exception of the lowest. For each of the amides, when k_1 (first-order rate constant) was plotted against alkali concentration, the resulting graph (4—7 points) was linear and passed through the origin. Typical results, for acetamide at 50°, are given in Table 1.

The linear plots of k_1 against [NaOH] are described by the equation $k_1 = k_2 . m_{NaOH}$. The "catalytic coefficient" of the hydroxyl ion (k_2) is the second-order rate constant for the bimolecular reaction between amide and hydroxyl ion. Relevant values for k_2, the activation energy (E), and the temperature-independent term of the Arrhenius equation ($\log_{10} B$) are given in Table 2, together with the estimated errors.

Aromatic Amides.—With each of these amides the distillation method of analysis was used, because of the extensive reaction between amide and hypobromite. Procedure for kinetic work at 70° was similar to that adopted for the aliphatic amides, at least four values for [NaOH] being used, and linear k_1–[NaOH] plots were again obtained. Kinetics at 80° were followed for all four amides but alkali concentrations were limited to 0·25—0·50M-sodium

TABLE 1.

[NaOH] (mole/l.)	10^3k_1 (50°) (min.$^{-1}$) Individual values				Mean
0·03125		0·5			0·5
0·0625		1·03	0·94		0·99
0·125		1·96	2·10		2·03
0·250	4·13	4·13	4·10	4·10	4·10
	4·10	4·25	4·08	3·94	
	4·07				
0·375		6·88	6·83		6·86
0·500	9·80	8·80	9·25	9·58	9·33
	9·58	9·75	9·10	8·80	
0·625	12·1	11·4	11·2	11·4	11·5

TABLE 2.

	10^3k_2 (l. mole^{-1} min.$^{-1}$) 50°	70°	E (± 0·5) (kcal. mole^{-1})	$\log_{10} B$ (± 0·24)
Acetamide	18·4 ± 0·2	66·8 ± 0·3	14·3	6·15
Propionamide	16·6 ± 0·1	60·2 ± 0·6	14·4	6·17
*iso*Butyramide	6·58 ± 0·1	25·5 ± 0·6	15·0	6·18
Trimethylacetamide	1·53 ± 0·02	6·35 ± 0·2	15·7	6·02

TABLE 3.

	10^3k_2 (±0·2) (at 70°)	10^3k_1 in 0·50M-NaOH 80°	70°	60°	E (±1)	$\log_{10} B$ (±0·5)
Benzamide	16·3	15·6	8·20	—	12	6·0
p-Toluamide	10·4	9·5	5·30	2·80	13	6·4
p-Ethylbenzamide	10·8	9·7	5·28	—	13	6·2
*p-iso*Propylbenzamide	10·6	9·1	4·80	—	12	5·5
p-tert.-Butylbenzamide	10·8	9·1	5·60	2·75	11	5·1

hydroxide. In view of the results obtained at these two temperatures the hydrolyses of *p*-toluamide and *p-tert.*-butylbenzamide were followed at 60° in 0·50M-sodium hydroxide. Relevant data are collected in Table 3.

Results.—The order of reactivity of the aliphatic amides is apparently determined by the

inductive effects of the alkyl groups, the effect of hyperconjugation on the order being small and almost negligible. Steric effects appear to be constant, there being no appreciable difference between frequency factors within the series. Similar results have been observed in the alkaline hydrolysis of the corresponding esters (Davies and Evans, *loc. cit.*). In the aromatic series there is no definite reactivity order. All four substituted benzamides are hydrolysed more slowly than the parent amide but there are no significant differences between the reaction rates of the *p*-alkylbenzamides, the observed differences in rate constants being just within the limits of experimental error. It thus appears that the order is a mixed inductive–hyperconjugative order displaying an unusual balance of effects.

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The Preparation and Properties of Tellurium Dibromide.

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A convenient method is given for the preparation of tellurium dibromide by the reaction between bromotrifluoromethane and molten tellurium. Some of its properties are described. It has been used to prepare tellurium(IV) dibromide di-iodide, diamminotellurium dibromide, and some pyridine complexes. Bromotrifluoromethane is converted into hexafluoroethane.

BERZELIUS (*Pogg. Ann.*, **1833**, **28**, 392; 1834, **32**, 1, 577) claimed to have obtained tellurium dibromide as a greenish-black crystalline mass by subliming a mixture of tellurium and tellurium tetrabromide. Carnelley and Williams (*J.*, 1880, **37**, 125), who do not describe their preparation, give for the dibromide m. p. 280° and b. p. 339°, but Brauner (*J.*, 1889, **55**, 382) found m. p. 210°. The latter prepared his material by fusing the tetrabromide with an excess of tellurium, followed by sublimation either in a vacuum or in a current of carbon dioxide. The product so obtained appeared sometimes as a black or blackish-green mass, sometimes as needles of a pale steel colour, and at other times as a black or olive-green powder.

Damiens (*Compt. rend.*, 1921, **173**, 300) showed that, although tellurium dibromide exists in the vapour state, there is no evidence of its existence on the freezing-point curve of mixtures of the constituent elements and, when normally prepared, the dibromide vapour, on condensation, decomposes to form a solid solution of the metal and its tetrabromide. On addition of ether to this product, the tetrabromide dissolves and leaves a residue of tellurium. However, later (*ibid.*, 1921, **173**, 583; *Ann. Chim.*, 1923, **19**, 44) Damiens isolated the true dibromide in the solid state (*a*) by cooling its vapour in a vacuum to −80°, and (*b*) by reducing the tellurium tetrabromide in dry ethereal solution in the dark with finely divided tellurium. The dibromide is chocolate-brown, and completely soluble in ether, from which solution it can be recovered unchanged. Disproportionation is rapid when the solid dibromide is gently heated, so Damiens was unable to determine its m. p. and b. p. He was able, however, to show that in ethereal solution tellurium dibromide combines with iodine to form red crystals of tellurium(IV) dibromide di-iodide, $TeBr_2I_2$.

It appears that other workers in this field have not handled solid tellurium dibromide but a solid solution of the element and its tetrabromide. *E.g.*, Yost and Hatcher (*J. Amer. Chem. Soc.*, 1932, **54**, 151), who have shown by vapour-density measurements that the molecule of the vapour is $TeBr_2$ up to 750°, describe tellurium dibromide as a black solid.

We describe a new method of preparing tellurium dibromide which consists of streaming bromotrifluoromethane over molten tellurium so as to obtain a black, amorphous powder which is the solid solution of tellurium in tellurium tetrabromide, and then subliming this mixture in a dry vacuum on to a surface cooled in liquid air. In this way chocolate-brown pure tellurium dibromide is deposited on the cooled surface and in a fair yield. Our product is identical with that obtained by Damiens.

From the unpleasant-smelling gaseous by-products, hexafluoroethane was isolated and in an amount expected from the reaction: $2CF_3Br + Te = C_2F_6 + TeBr_2$.

The dibromide thus obtained has a vapour which is violet at lower temperatures and pink at higher temperatures. It is readily soluble in dry diethyl ether and less readily in dry chloroform, and forms greenish-yellow solutions; these solutions are unstable and, at ordinary temperatures, tellurium is slowly deposited from them on to the walls of the containing vessel. This decomposition is accelerated if the solutions are heated; and, if a trace of moisture is admitted, the decomposition is instantaneous. In each case the solution remaining is tellurium tetrabromide.

The solid solution of tellurium in its tetrabromide was found to have m. p. 279—281° and b. p. 340°, figures in good agreement with those published by Carnelley and Williams (*loc. cit.*) for the dibromide. It seems, therefore, that their material was the solid solution and not the dibromide.

In fluorine much diluted with nitrogen, tellurium dibromide reacts at once to form first the tetrafluoride and then the hexafluoride. No evidence of a difluoride has been obtained. When the dibromide is gently heated in chlorine, bromine is liberated and black tellurium dichloride is formed which is then oxidised to the tetrachloride. Liquid bromine converts the dibromide exothermally into the tetrabromide. When ethereal solutions of the dibromide and iodine are mixed in a dry evacuated vessel, and some of the ether is then evaporated from the mixture, garnet-red crystals of tellurium(IV) dibromide di-iodide crystallise, having m. p. 323—325°, b. p. 420° (decomp.). The liquid is dark red, the vapour purple. Like the tetrabromide, the compound is unaffected by dry air but slowly absorbs moisture from the atmosphere. Water decomposes it at once with the formation of a white precipitate of tellurous acid in hydrobromic and hydriodic acids.

When ethereal solutions of tellurium(IV) dibromide di-iodide and pyridine are mixed, a new complex, dipyridinedibromodi-iodotellurium(IV), $(C_5H_5N)_2TeBr_2I_2$, is precipitated as an amorphous cream-coloured powder. It is stable in dry air, but becomes yellow in moist air, and is at once hydrolysed by water to tellurous acid.

Dipyridinedibromodi-iodotellurium(IV) dissolves in warm concentrated hydrochloric, hydrobromic, and hydriodic acid to give, on cooling, orange needles of dipyridinium dibromodichlorodi-iodotellurite, $(C_5H_5NH)_2TeCl_2Br_2I_2$, red needles of dipyridinium tetrabromodi-iodotellurite $(C_5H_5NH)_2TeBr_4I_2$, and black needles of dipyridinium hexaiodotellurite, $(C_5H_5NH)_2TeI_6$, respectively.

When ethereal solutions of tellurium dibromide and pyridine are mixed a white solid is first precipitated which rapidly blackens, precipitating tellurium and leaving dipyridinetetrabromotellurium(IV), $(C_5H_5N)_2TeBr_4$.

Tellurium dibromide does not combine with either gaseous or liquid sulphur dioxide or with hydrogen cyanide, but it disproportionates in each of the liquids. Dry ammonia, however, at laboratory temperatures is at first rapidly absorbed by tellurium dibromide and then much more slowly. The black powder remaining when the excess of ammonia is removed is diamminotellurium dibromide, $TeBr_2,2NH_3$, which is unaffected by air but loses ammonia when heated alone or with sodium hydroxide. In liquid ammonia the dibromide blackens, swells to a bulky mass, and with further liquid collapses to a black powder containing free tellurium and tellurium nitride. The liquid ammonia contains ammonium bromide. In this reaction the tellurium dibromide probably disproportionates and the tetrabromide formed then undergoes ammonolysis to form tellurium nitride (Strecker and Ebert, *Ber.*, 1925, **58**, 2527).

Experimental

Preparation of Tellurium Dibromide.—Bromotrifluoromethane (from Imperial Chemical Industries Limited), dried with concentrated sulphuric acid and then with phosphoric oxide, was led over molten tellurium at about 500°. The disproportionation mixture of tellurium and tellurium tetrabromide was formed as a black, amorphous powder and was distilled forward in the gas stream and collected in the first of two receivers. The flow of gas was stopped and the receivers were sealed off from the rest of the apparatus and evacuated. On distillation of

the mixture of tellurium and its tetrabromide into the second receiver, which contained a surface cooled in liquid air, tellurium dibromide collected on the cold surface as a chocolate-brown, amorphous powder. Its vapour was violet at lower temperatures and pink at higher temperatures. It was unstable, and if it was heated gently or if a trace of water was admitted, it disproportionated at once, forming the black solid solution of the metal in its tetrabromide. The dibromide was completely soluble in ether, but the solution rapidly precipitated tellurium when exposed to light or boiled or when treated with a trace of moisture. It was less soluble in chloroform, and solutions in this solvent were also unstable, but the deposition of tellurium by light was slower.

When the gas issuing from the reaction vessel was cooled to approx. −180° (bromotrifluoromethane has b. p. −59°), a colourless foul-smelling liquid containing traces of tellurium was collected. The tellurium was removed from this liquid by passing its vapour through "Carbosorb" and then into a trap surrounded by liquid air. The contents of the trap were transferred to the bottom of a Podbielniak-type low-temperature fractionation column (Podbielniak, *Ind. Eng. Chem. Anal.*, 1931, **3**, 177) and fractionated, and the amounts and molecular weights of the fractions were determined. Unchanged bromotrifluoromethane and hexafluorethane, b. p. −78° (lit., −78°), made up the whole of the fractionated liquid (Found: *M*, 138·5. Calc. for C_2F_6: *M*, 138).

Reactions with Halogens.—Tellurium dibromide reacted spontaneously in fluorine diluted with nitrogen (1 : 10, by vol.) and the surface of the solid was soon coated with the tetrafluoride. On continued flow of fluorine, the tetrafluoride was rapidly oxidised to gaseous tellurium hexafluoride.

Chlorine rapidly converted gently heated tellurium dibromide first into the black dichloride and then into the tetrachloride with the liberation of bromine.

Excess of liquid bromine was added to a few g. of tellurium dibromide. A strongly exothermic reaction took place. On removal of the excess of bromine in a stream of carbon dioxide, yellow tellurium tetrabromide remained.

Mixing ethereal solutions of tellurium dibromide and iodine in an evacuated vessel and then evaporating away some of the excess of ether gave garnet-red crystals of tellurium(IV) dibromide di-iodide (Found: Te, 23·7; Br, 29·9; I, 46·6. Calc. for $TeBr_2I_2$: Te, 23·6; Br, 29·5; I, 46·9%), m. p. 323—325°, b. p. 420°. Decomposition with liberation of iodine takes place on boiling.

Pyridine Complexes of $TeBr_2I_2$.—This compound (1 mol.) and pyridine (2 mols.) were mixed in ether. *Dipyridinedibromodi-iodotellurium*(IV) was precipitated as a cream-coloured amorphous solid in almost quantitative yield [Found: C, 17·5; N, 3·6; H, 1·8; Te, 18·2; Br, 23·8; I, 35·5. $(C_5H_5N)_2TeBr_2I_2$ requires C, 17·2; N, 4·0; H, 1·4; Te, 18·3; Br, 22·9; I, 36·4%]. This compound is at once hydrolysed by water to tellurous acid. It melts with decomposition and, when it is boiled, pyridine and iodine are evolved.

Dipyridinedibromodi-iodotellurium(IV) (I) was dissolved in hot concentrated hydrochloric acid and, on cooling, orange needles of *dipyridinium dibromodichlorodi-iodotellurite* (II) crystallised [Found: C, 16·0; N, 3·8; H, 1·5; Te, 16·4; Cl, 9·6; Br, 20·3; I, 33·7. $(C_5H_5NH)_2TeCl_2Br_2I_2$ requires C, 15·5; N, 3·6; H, 1·6; Te, 16·5; Cl, 9·2; Br, 20·7; I, 32·9%]; the compound (I) in hot concentrated hydrobromic acid gave red needles of *dipyridinium tetrabromodi-iodotellurite* (III) on cooling [Found: C, 13·3; N, 3·7; H, 1·1; Te, 15·1; Br, 36·9; I, 30·3. $(C_5H_5NH)_2TeBr_4I_2$ requires C, 13·9; N, 3·3; H, 1·4; Te, 14·8; Br, 37·5; I, 29·5%]. The compounds (I), (II), and (III) with hydrogen iodide gave in each case dipyridinium hexaiodotellurite $(C_5H_5NH)_2TeI_6$, which is the most stable compound of this series (Aynsley and Hetherington, *J.*, 1953, 2802) [Found: C, 11·6; N, 2·8; H, 1·3; Te, 12·2; I, 72·3. Calc. for $(C_5H_5NH)_2TeI_6$: C, 11·4; N, 2·7; H, 1·1; Te, 12·1; I, 72·7%].

When ethereal solutions of tellurium dibromide and pyridine were mixed, a white amorphous solid was first precipitated but this at once blackened, depositing tellurium and dipyridinetetrabromotellurium(IV). A little of this was separated from the tellurium by extraction with hot pyridine and was readily identified by dissolving it in hot concentrated hydrobromic acid and crystallising out red needles of dipyridinium hexabromotellurite [Found: C, 15·8; N, 3·6; H, 1·7; Te, 16·8; Br, 62·3. Calc. for $(C_5H_5NH)_2TeBr_6$: C, 15·7; N, 3·7; H, 1·6; Te, 16·6; Br, 62·6%].

Reaction with Ammonia.—(*a*) A stream of dry ammonia was passed over tellurium dibromide at laboratory temperature. The dibromide blackened and absorption of the ammonia was rapid at first, but the reaction was not complete until the dibromide and gas had been in contact for several days. On removal of the excess of ammonia with dry nitrogen followed by exposure

-CO·C'C·CO- In terms of either the generally accepted formula (I) or the modified

to phosphoric oxide in a desiccator, *diamminotellurium dibromide*, $Te(NH_2)_2Br_2$, was obtained as an amorphous black powder, unchanged when exposed to air, but readily losing ammonia when heated alone or with sodium hydroxide [Found : Te, 39·8; N, 9·0; H, 1·8; Br, 49·5. $Te(NH_2)_2Br_2$ requires Te, 39·7; N, 8·8; H, 1·9; Br, 49·7%]. (*b*) A quantity of tellurium dibromide was transferred to a fritted-glass filter in an evacuated Pyrex vessel and cooled to $-50°$ (NH_3 has b. p. $-33·5°$), and then ammonia was led in. The dibromide became black and at first the gas was rapidly absorbed by the dibromide, which swelled gently, but when liquid ammonia began to appear in the vessel the bulky solid collapsed to a fine black solid on the filter. The filtrate passing through left ammonium bromide on evaporation of the excess of ammonia, and the black residue on the filter was mainly tellurium mixed with tellurium nitride. The latter was recognised by its liberation of ammonia in warm sodium hydroxide and its explosive decomposition into its elements when dried and heated.

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KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, March 30th*, 1955.]

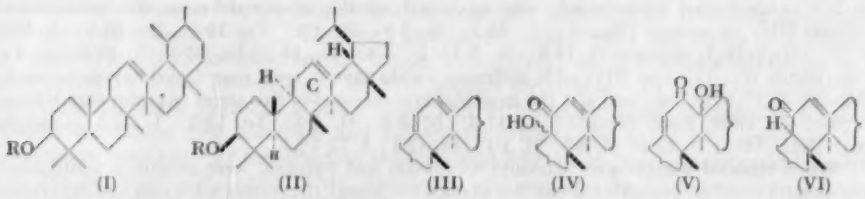
Triterpenoids. Part XXXVIII. Ursa-9(11) : 13(18)-dien-3β-yl Acetate.*

By J. M. BEATON, J. I. SHAW, F. S. SPRING, ROBERT STEVENSON, W. S. STRACHAN, and J. L. STEWART.

[Reprint Order No. 6218.]

Oxidation of ursa-9(11) : 12-dien-3β-yl acetate (III; R = Ac) with chromic acid gives a mixture from which two homogeneous products have previously been isolated. These have now been identified as 3β-acetoxy-9ξ-hydroxyurs-12-en-11-one (IV) and 13ξ : 18ξ-epoxy-12-oxours-9(11)-en-3β-yl acetate (VII). Reduction of the latter compound with zinc dust gives 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate (VIII), catalytic hydrogenation of which yields ursa-9(11) : 13(18)-dien-3β-yl acetate (IX).

URSA-9(11) : 12-DIEN-3β-YL ACETATE (III) is obtained from α-amyrin acetate (II) † by a number of methods, the most convenient of which is oxidation with *N*-bromosuccinimide (Ruzicka, Jeger, and Redel, *Helv. Chim. Acta*, 1943, **26**, 1235). Oxidation of the homoannular dienyl acetate (III) with chromic acid gives an acetate, $C_{32}H_{50}O_4$, in which the presence of an αβ-unsaturated ketone group and a tertiary hydroxyl group has been



(I) (II) (III) (IV) (V) (VI)

established, and which was formulated as (IV) or (V) (Beynon, Sharples, and Spring, *J.*, 1939, 1233). The oxidation of ursa-9(11) : 12-dien-3β-yl acetate was repeated by Ruzicka, Jeger, Redel, and Volli (*Helv. Chim. Acta*, 1945, **28**, 199) who obtained, in addition to the acetate $C_{32}H_{50}O_4$, a second acetate $C_{32}H_{48}O_4$, which they suggested contains the group

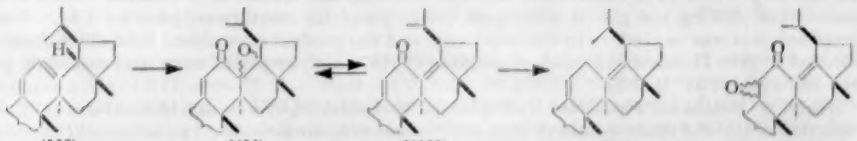
* Part XXXVII, *J.*, 1955, 2131.

† In this paper we use the expression (II; R = H) to represent the constitution and stereochemistry of α-amyrin. The reasons for the adoption of this formula in place of the hitherto accepted formula (I; R = H) are given in the following paper. In all formulæ, R = Ac unless otherwise stated.

–CO·C:C·CO–. In terms of either the generally accepted formula (I) or the modified formula (II) for α-amyrin acetate, it is impossible to formulate such an ene-dione unless molecular rearrangement is assumed during the oxidation of ursa-9(11) : 12-dien-3β-yl acetate.

We have re-examined the products obtained by oxidation of the dienyl acetate (III) with chromic acid. From the mixture we had no difficulty in isolating the two homogeneous acetates, $C_{32}H_{50}O_4$ and $C_{32}H_{48}O_4$. Treatment of the former with zinc dust and acetic acid gave 11-oxours-12-en-3β-yl acetate (VI) in excellent yield, from which it follows that the parent acetate is 3β-acetoxy-9ξ-hydroxyurs-12-en-11-one (IV). Ruzicka *et al.* (*loc. cit.*) found that treatment of the acetate $C_{32}H_{50}O_4$ with strong alkali at 200—210°, followed by acetylation, gave a mixture of two products, one of which was formulated as $C_{32}H_{48}O_3$, *i.e.*, as a dehydration product of the parent acetate, $C_{32}H_{50}O_4$. We noted that the properties of this product {m. p. 285—286°, $[\alpha]_D$ +93°, $\lambda_{max.}$ 2480 Å (log ε 4·05), no colour with tetranitromethane} are very similar to those of 11-oxours-12-en-3β-yl acetate, $C_{32}H_{50}O_3$ (VI) {m. p. 284—285°, $[\alpha]_D$ +98°, $\lambda_{max.}$ 2480 Å (ε 12,000), no colour with tetranitromethane}. Repetition of the experiment showed that this product is indeed 11-oxours-12-en-3β-yl acetate, and its formation is to be ascribed to a reduction, and not to a dehydration, of the parent acetate (IV).

The second acetate, $C_{32}H_{48}O_4$, obtained by oxidation of ursa-9(11) : 12-dien-3β-yl acetate with chromic acid, has now been identified as 13ξ : 18ξ-epoxy-12-oxours-9(11)-en-3β-yl acetate (VII). When reduced in ethanol solution with zinc, it gives 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate (VIII), characterised by hydrolysis to the corresponding alcohol (VIII; R = H). Surprisingly, the same reduction is achieved by using lithium in liquid ammonia. Conversely, oxidation of 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate (VIII) with chromic acid gives the epoxide (VII). The acetate (VIII) shows absorption maxima



at 2080, 2620, and 2940 Å (ε 7900, 9300, and 7700) and in this respect it is very similar to 12-oxo-oleana-9(11) : 13(18)-dien-3β-yl acetate (Beaton, Johnston, McKean, and Spring, *J.*, 1953, 3660), the absorption spectrum of which shows maxima at 2080, 2600, and 2950 Å (ε 9000, 9250, and 8450). This characteristic absorption spectrum of 12-oxo-oleana-9(11) : 13(18)-dien-3β-yl acetate has been attributed to the geometry of its >C:C·CO·C:C< chromophore; in contrast, compounds containing the same chromophore in a 6-membered ring show an absorption maximum at *ca.* 2400 Å.

The oxygen atom removed from the acetate $C_{32}H_{48}O_4$ by treatment with zinc dust is an oxidic function because the infrared absorption spectrum of (VII) includes bands attributable to the acetate group and the αβ-unsaturated carbonyl group, but it does not include bands due to the presence of either a hydroxyl or an isolated ketone group. Of the alternative constitutions (VII) and (VII*a*) for the acetate $C_{32}H_{48}O_4$, which shows an absorption maximum at 2570 Å, we prefer the former, for two reasons. First, the acetate $C_{32}H_{48}O_4$ is recovered unchanged after treatment with hydrochloric–acetic acid; the secondary-tertiary oxide group in (VII*a*) would not, in our opinion, survive this treatment. Secondly, the intensity of its ultraviolet absorption band is not consonant with the presence of a *cisoid* αβ-unsaturated ketone as in (VII*a*).

Catalytic hydrogenolysis of 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate (VIII) gives the non-conjugated ursa-9(11) : 13(18)-dien-3β-yl acetate (IX) which does not show high-intensity selective absorption above 2200 Å. It does, however, show strong ethylenic absorption between 2100 and 2200 Å and gives a colour with tetranitromethane. The non-conjugated dienyl acetate (IX) was characterised by alkaline hydrolysis to the corresponding alcohol (IX; R = H).

Experimental

Rotations were measured in chloroform and ultraviolet absorption spectra in EtOH solutions. Grade II alumina and light petroleum, b. p. 60—80°, were used for chromatography.

Oxidation of Ursa-9(11) : 12-dien-3β-yl Acetate (III) *with Chromic Acid.*—A solution of chromium trioxide (8 g.) in water (8 c.c.) and acetic acid (80 c.c.) was added during 20 min. with vigorous stirring to a solution of ursa-9(11) : 12-dienyl acetate (8·0 g.) in glacial acetic acid (300 c.c.). The mixture was refluxed for 2 hr., treated with methanol, concentrated under reduced pressure, and diluted with water. During the ether-extraction of the mixture, a solid remained suspended in the ether layer. This was collected and crystallised from chloroform–methanol to give 3β-acetoxy-9ξ-hydroxyurs-12-en-11-one (IV) as blades (1·3 g.), m. p. 315—317°, $[\alpha]_D$ +55° (*c*, 2·2), $\lambda_{max.}$ 2500 Å (ε 13,500) (Found: C, 77·3; H, 10·3. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%). It does not give a colour with tetranitromethane. Beynon, Sharples, and Spring (*loc. cit.*) give m. p. 312°, $[\alpha]_D$ +61°; Ruzicka, Jeger, Redel, and Volli (*loc. cit.*) give m. p. 316° (high vac.), $[\alpha]_D$ +62°, for this compound.

The ether extract was evaporated and the residue crystallised from chloroform–methanol to give the diol monoacetate (IV) (200 mg.), m. p. and mixed m. p. 315—317°. Concentration of the chloroform–methanol mother-liquors yielded 13ξ : 18ξ-*epoxy*-12-*oxours*-9(11)-*en*-3β-*yl acetate* (VII) which, after recrystallisation from the same solvent, separated as plates (500 mg.), m. p. 269—271°, $[\alpha]_D$ +71° (*c*, 1·1), $\lambda_{max.}$ 2570 Å (ε 13,000) (Found: C, 77·7; H, 9·6. $C_{32}H_{48}O_4$ requires C, 77·4; H, 9·7%). Infrared absorption: Bands at 1250 and 1722 (acetate), 1603 and 1652 cm.$^{-1}$ (αβ-unsaturated ketone), no hydroxyl band. It does not give a colour with tetranitromethane. Ruzicka, Jeger, Redel, and Volli (*loc. cit.*) give m. p. 258°, $[\alpha]_D$ +70°, $\lambda_{max.}$ 2590 Å (log ε 4·1), for a compound $C_{32}H_{48}O_4$ obtained by the same method. The oxide (120 mg.) was recovered unchanged after being heated on the steam-bath for 1 hr. with acetic acid (15 c.c.) and concentrated hydrochloric acid (0·5 c.c.).

Action of Zinc Dust on 3β-*Acetoxy*-9ξ-*hydroxyurs*-12-*en*-11-*one* (IV).—Zinc dust (4·3 g.) (activated by warm 10% ammonium chloride solution) was added to a solution of the diol monoacetate (600 mg.) in glacial acetic acid (50 c.c.) and the mixture refluxed for 1 hr. The filtered solution was worked up in the usual way, and the product crystallised from chloroform–methanol to give 11-oxours-12-en-3β-yl acetate (VI) (570 mg.) as plates, m. p. and mixed m. p. 284—285°, $[\alpha]_D$ +98° (*c*, 1·2).

Action of Methanolic Potassium Hydroxide on 3β-*Acetoxy*-9ξ-*hydroxyurs*-12-*en*-11-*one* (IV).—A solution of the diol monoacetate (3·0 g.) and potassium hydroxide (12 g.) in methanol (120 c.c.) was heated at 175° for 6 hr. The product, isolated through ether, was acetylated by pyridine and acetic anhydride at 100°. The acetylated product crystallised from chloroform–methanol to yield a *substance* (900 mg.) as needles, m. p. 169—171°, $[\alpha]_D$ −60° (*c*, 1·1), ε 9800 at 2080 Å (Found: C, 76·6; H, 10·4. $C_{32}H_{50}O_4$ requires C, 77·1; H, 10·1; $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·5%). It gives a pale yellow colour with tetranitromethane. Concentration of the mother-liquor gave 11-oxours-12-en-3β-yl acetate (VI) as plates (1·4 g.), m. p. and mixed m. p. 285°, $[\alpha]_D$ +98° (*c*, 0·9), $\lambda_{max.}$ 2480 Å (ε 12,250); this does not give a colour with tetranitromethane.

12-*Oxoursa*-9(11) : 13(18)-*dien*-3β-*yl Acetate* (VIII).—(*a*) Zinc dust (10 g.; activated by boiling acetic acid or warm 10% ammonium chloride solution) was added to a solution of 13ξ : 18ξ-epoxy-12-oxours-9(11)-en-3β-yl acetate (VII) (500 mg.) in ethanol (250 c.c.), and the mixture refluxed for 5 hr. Evaporation of the filtered solution gave a yellow solid, which crystallised from methanol as pale yellow plates, m. p. 202—204°, $[\alpha]_D$ −42° (*c*, 1·8). Recrystallisation from the same solvent yielded 12-*oxoursa*-9(11) : 13(18)-*dien*-3β-*yl acetate* as pale yellow plates (430 mg.), m. p. 203—205°, $[\alpha]_D$ −43° (*c*, 2·0), $\lambda_{max.}$ 2080, 2620, and 2940 Å (ε 7900, 9300, and 7700) (Found: C, 79·8; H, 10·0. $C_{32}H_{48}O_3$ requires C, 79·95; H, 10·1%). The m. p. of this compound is variable (±4°) and is a poor criterion of purity. A mixture with 12-oxo-oleana-9(11) : 13(18)-dien-3β-yl acetate (m. p. 205—207°) had m. p. 172—179°. Zinc dust reduction of (VII) in refluxing acetic acid (instead of ethanol) gave a mixture from which, after chromatography, poor yields of ursa-9(11) : 13(18)-dien-3β-yl acetate (IX) (see later) and 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate (VIII) were isolated.

(*b*) A solution of 13ξ : 18ξ-epoxy-12-oxours-9(11)-en-3β-yl acetate (VII) (500 mg.) in dry ether (15 c.c.) and dry dioxan (10 c.c.) was added with vigorous stirring during 2 min. to a solution of lithium (150 mg.) in liquid ammonia (100 c.c.). After a further 3 min., acetone was added and the ammonia allowed to evaporate. The residue was acetylated by pyridine and acetic anhydride at room temperature for 15 hr., and the acetylated product chromatographed on

alumina (15 g.). Benzene–light petroleum (1 : 9) eluted a fraction which crystallised from chloroform–methanol as needles (20 mg.), m. p. 170—172°, $[\alpha]_D$ +156° (*c*, 0·7). It has no selective light absorption above 2000 Å and does not give a colour with tetranitromethane. The fraction eluted by benzene–light petroleum (1 : 1) crystallised from aqueous methanol to give 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate as pale yellow plates (210 mg.), m. p. and mixed m. p. 203—205°, $[\alpha]_D$ −44° (*c*, 0·8), $\lambda_{max.}$ 2080, 2620, and 2940 Å (ε 9600, 10,000, and 8100).

Treatment of 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate with lithium and liquid ammonia gave unchanged starting material together with a small quantity of a product, m. p. 170—172°, $[\alpha]_D$ +157° (*c*, 0·9). It was undepressed in m. p. when mixed with the compound of the same m. p. described above.

12-Oxoursa-9(11) : 13(18)-dien-3β-yl acetate was recovered unchanged after treatment with (*a*) sodium borohydride in aqueous methanol at room temperature, and (*b*) glacial acetic acid (8 parts) and concentrated hydrochloric acid (1 part) at 100° for 18 hr.

12-*Oxoursa*-9(11) : 13(18)-*dien*-3β-*ol* (VIII; R = H).—Hydrolysis of the acetate by 3% aqueous-methanolic potassium hydroxide, and crystallisation of the product from aqueous methanol gave 12-*oxoursa*-9(11) : 13(18)-*dien*-3β-*ol* as faintly yellow prismatic needles, m. p. 222—223°, $[\alpha]_D$ −73° (*c*, 0·9), $\lambda_{max.}$ 2080, 2630, and 2950 Å (ε 8050, 9600, and 7900) (Found: C, 82·1; H, 10·6. $C_{30}H_{46}O_3$ requires C, 82·1; H, 10·6%). Reacetylation by pyridine and acetic anhydride at 100° gave the parent acetate as yellow plates (from methanol), m. p. and mixed m. p. 202—203°, $[\alpha]_D$ −43° (*c*, 0·9).

Oxidation of 12-*Oxoursa*-9(11) : 13(18)-*dien*-3β-*yl Acetate* (VIII) *with Chromic Acid*.—A solution of chromium trioxide (18·8 mg.) in glacial acetic acid (4·0 c.c.) was added to a solution of 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate (75 mg.) in acetic acid (15 c.c.), and the mixture set aside at room temperature for 18 hr., then heated on the steam-bath for 1 hr. The mixture was worked up in the usual way and the product chromatographed on alumina (3 g.). Elution with light petroleum and benzene yielded amorphous fractions. Methanol–benzene (1 : 9) eluted a solid which crystallised from methanol to give 13ξ : 18ξ-epoxy-12-oxours-9(11)-en-3β-yl acetate (VII) (35 mg.) as plates, m. p. and mixed m. p. 266—269°, $[\alpha]_D$ +69·5° (*c*, 0·7), $\lambda_{max.}$ 2580 Å (ε 11,400).

Hydrogenolysis of 12-*Oxoursa*-9(11) : 13(18)-*dien*-3β-*yl Acetate* (VIII).—A solution of 12-oxoursa-9(11) : 13(18)-dien-3β-yl acetate (300 mg.) in glacial acetic acid was shaken with platinum (from 200 mg. of PtO_2) in hydrogen for 4½ hr. After removal of the catalyst and solvent, the product was crystallised from chloroform–methanol to give *ursa*-9(11) : 13(18)-*dien*-3β-*yl acetate* (IX) as plates (260 mg.), m. p. 193—194°, $[\alpha]_D$ +72° (*c*, 1·8), ε 9150 at 2140 Å (Found: C, 82·7; H, 10·6. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%). It gives an orange colour with tetranitromethane. A mixture with oleana-9(11) : 13(18)-dienyl acetate, m. p. 196—197°, had m. p. 184—188°.

Ursa-9(11) : 13(18)-*dien*-3β-*ol* (IX; R = H).—Hydrolysis of the acetate in the usual way by 3% aqueous-methanolic potassium hydroxide and recrystallisation of the product successively from methanol, light petroleum (b. p. 60—80°), and methanol gave *ursa*-9(11) : 13(18)-*dien*-3β-*ol* as blades, m. p. 189—190°, $[\alpha]_D$ +61° (*c*, 0·9) (Found: C, 84·3; H, 11·7. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). It gives an orange colour with tetranitromethane. Reacetylation gave ursa-9(11) : 13(18)-dien-3β-yl acetate as plates (from chloroform–methanol), m. p. and mixed m. p. 193—194°, $[\alpha]_D$ +73° (*c*, 1·8).

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Triterpenoids. Part XXXIX. The Constitution and Stereochemistry of the Ursane Group of Triterpenoids.*

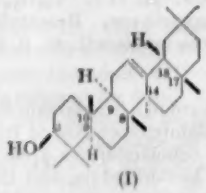
By J. M. Beaton, F. S. Spring, Robert Stevenson, and W. S. Strachan.

[Reprint Order No. 6219.]

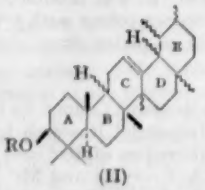
The dienyl acetate obtained by oxidation of α-amyrin acetate with selenium dioxide has been identified as ursa-11 : 13(18)-dien-3β-yl acetate. Its dihydro-derivative, urs-13(18)-en-3β-yl acetate, is isomerised by sulphuric acid to α-amyrin acetate. Ursa-9(11) : 13(18)-dien-3β-yl acetate (XII) is isomerised by mineral acid to oleana-11 : 13(18)-dien-3β-yl acetate (VII). This is the first instance of the conversion of a simple ursane derivative into an isomer belonging to another triterpenoid group. The isomerisation proceeds *via* ursa-11 : 13(18)-dien-3β-yl acetate which is also isomerised by mineral acid to oleana-11 : 13(18)-dien-3β-yl acetate (VII), as is ursa-9(11) : 12-dien-3β-yl acetate. The rearrangements prove that α-amyrin and β-amyrin have the same configurations at positions 3, 5, 8, 9, 10, 14, and 17. These rearrangements and other reactions of members of the ursane group lead to the view that the constitution and stereochemistry of α-amyrin are represented by the expression (XV).

The constitution and stereochemistry of β-amyrin (olean-12-en-3β-ol) shown in (I) are supported by a wealth of experimental evidence (for literature see Jeger, " Fortschritte der Chemie der organischer Naturstoffe," Springer-Verlag, 1950, Vol. VII, p. 1; Barton and Holness, *J.*, 1952, **78**; Barton, *J.*, 1953, 1027); they are as secure as is possible without the added support of total synthesis. Very different is the state of knowledge concerning the chemistry of α-amyrin (urs-12-en-3β-ol) and its relatives. In particular, the stereochemistry of the ursane group lacks clear definition, a circumstance well illustrated by the fact that, during the last two years, each of the four theoretically possible arrangements for the locking of rings D and E have been included in representations of the stereochemistry of α-amyrin (Ruzicka, *Experientia*, 1953, **9**, 357; Corey and Ursprung, *Chem. and Ind.*, 1954, 1387; Beton and Halsall, *ibid.*, p. 1560; Zürcher, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2149).

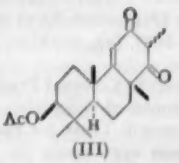
When the work described in this paper commenced, the constitution of α-amyrin was considered to be adequately expressed by (II; R = H).† The configurations at $C_{(3)}$, $C_{(5)}$, $C_{(8)}$, and $C_{(10)}$ in α-amyrin were established by its conversion into two enol ethers, derived from the diketone (III), which were also obtained by a series of parallel reactions from β-amyrin (I) (for literature see Jeger, *loc. cit.*). In addition, comparative studies on



(I)



(II)



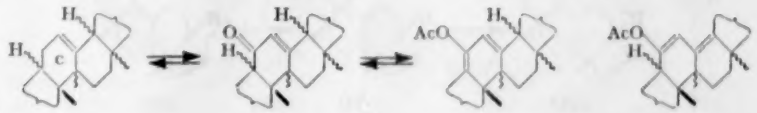
(III)

oleanane and ursane derivatives suggested that configuration at $C_{(9)}$ in both groups is identical (Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1075) although these did not constitute an absolute proof.

Our first approach to a clearer definition of the stereochemistry of α-amyrin was directed towards $C_{(9)}$. A cogent reason for the view that this centre has the more stable configuration is that 11-oxours-12-en-3β-yl acetate (IV), which is obtained by oxidation of

* Part XXXVIII, preceding paper.
† In the formulæ (II)—(XVII), R = Ac unless otherwise specified.

α-amyrin acetate with chromic acid (Spring and Vickerstaff, *J.*, 1937, 249) and is reduced catalytically to α-amyrin acetate (II) (Ruzicka, Leuenberger, and Schellenberg, *Helv. Chim. Acta*, 1937, **20**, 1271), is recovered unchanged after prolonged heating with strong alkali followed by reacetylation. A similar observation has been made with the related methyl 11-oxours-12-en-3β-olate acetate (Barton and Holness, *loc. cit.*). Another proof that $C_{(9)}$ in α-amyrin has the more stable configuration is now presented. 11-Oxours-12-en-3β-yl acetate (IV) gives an enol acetate which is strongly dextrorotatory ($[\alpha]_D$ +275°) and shows an absorption maximum at 2760 Å (ε 8000). 9(11) : 12-Dienes in the oleanane and ursane series show a similarly strong dextrorotation and an absorption maximum at approximately 2800 Å (ε *ca.* 9000). In contrast, 11 : 13(18)-dienes in the oleanane series are lævorotatory and are characterised by an intense triplet absorption curve, the major peak of which is at approximately 2500 Å (ε *ca.* 30,000). These facts show that the enol acetate from 11-oxours-12-en-3β-yl acetate is 3β : 11-diacetoxyursa-9(11) : 12-diene (V) and not the heteroannular isomer (VI). Hydrolysis of the enol acetate (V), by either acid or alkali, followed by acetylation of the product, gives 11-oxours-12-en-3β-yl acetate (IV) in excellent yield.

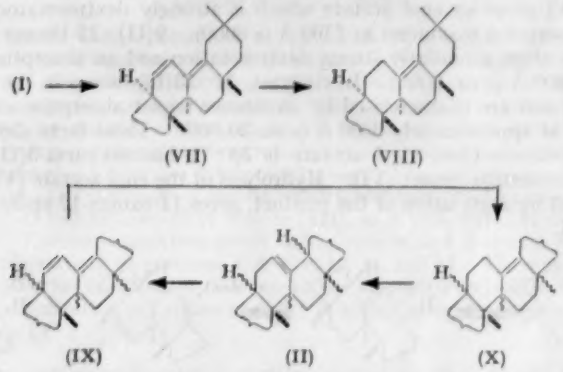


(II) (IV) (V) (VI)

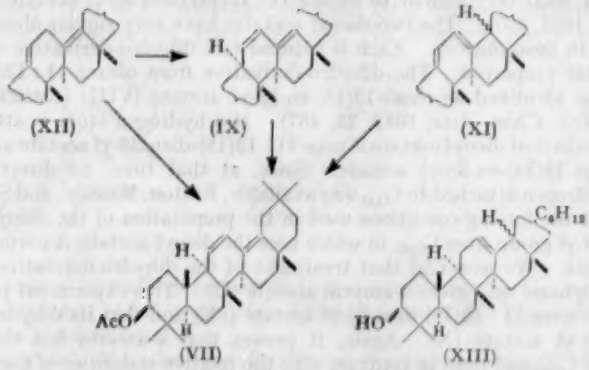
We next turned to a consideration of configuration at $C_{(18)}$ in α-amyrin. Whereas 11-oxo-olean-12-en-3β-yl benzoate is easily isomerised (and hydrolysed), by treatment with concentrated alkali, to give 11-oxo-18α-olean-12-en-3β-ol (Budziarek, Manson, and Spring, *J.*, 1951, 3336), similar treatment of 11-oxours-12-en-3β-yl acetate does not change the configuration at $C_{(18)}$. The related observation that reaction of methyl 11-oxours-12-en-3β-olate acetate with strong alkali does not cause inversion at $C_{(18)}$ has led to the conclusion that either the configuration at this centre is the more stable arrangement or there is no hydrogen attached to $C_{(18)}$ (Barton and Holness, *loc. cit.*). An alternative explanation of the failure of these αβ-unsaturated ketones to invert at $C_{(18)}$ with alkali, is that enolisation is directed towards $C_{(9)}$ exclusively. A proof of the stability of the configuration at $C_{(18)}$ in α-amyrin was found in the following way. Oxidation of α-amyrin acetate with selenium dioxide under forcing conditions gives, in low yield, a dienyl acetate (Easton, Manson, and Spring, *J.*, 1953, 943) very similar to oleana-11 : 13(18)-dien-3β-yl acetate (VII) (Barton and Brooks, *J.*, 1951, 257). The two dienyl acetates have very similar absorption spectra and they are both lævorotatory. Each is reduced to a dihydro-derivative and these also have very similar properties. The dihydro-derivative from oleana-11 : 13(18)-dien-3β-yl acetate has been identified as olean-13(18)-en-3β-yl acetate (VIII) (Ruzicka, Jeger, and Norymberski, *Helv. Chim. Acta*, 1942, **25**, 457). If a hydrogen atom is attached to $C_{(18)}$ in α-amyrin, the derived dienyl acetate is ursa-11 : 13(18)-dien-3β-yl acetate and its dihydro-derivative is urs-13(18)-en-3β-yl acetate. Since, at that time, no direct proof of the presence of a hydrogen attached to $C_{(18)}$ was available, Easton, Manson, and Spring (*loc. cit.*) emphasised that the forcing conditions used in the preparation of the dienyl acetate may eliminate a methyl group from $C_{(18)}$, in which case the dienyl acetate is norursa-11 : 13(18)-dien-3β-yl acetate. We now find that treatment of the dihydro-derivative of the dienyl acetate with sulphuric acid gives α-amyrin acetate (II). This experiment proves that the dienyl acetate is ursa-11 : 13(18)-dien-3β-yl acetate (IX) and that its dihydro-derivative is urs-13(18)-en-3β-yl acetate (X). Again, it proves that α-amyrin has the more stable configuration at $C_{(18)}$ and that, in contrast with the relative stabilities of the corresponding oleanane derivatives (Ames, Halsall, and Jones, *J.*, 1951, 450), urs-12-en-3β-yl acetate is thermodynamically more stable than urs-13(18)-en-3β-yl acetate. Finally it proves that ursa-11 : 13(18)-dien-3β-yl acetate and α-amyrin have the same configuration at $C_{(9)}$.

Three ursadien-3β-yl acetates have been prepared and characterised. These are the

homoannular ursa-9(11) : 12-dien-3β-yl acetate (XI) (Ewen, Spring, and Vickerstaff, *J.*, 1939, 1303), the heteroannular ursa-11 : 13(18)-dien-3β-yl acetate (IX), discussed above, and the non-conjugated ursa-9(11) : 13(18)-dien-3β-yl acetate (XII) described in the preceding paper. The three corresponding oleanadien-3β-yl acetates are known and, of these, the 11 : 13(18)-dienyl acetate is thermodynamically the most stable since it is obtained from



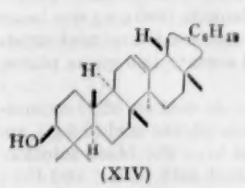
the isomeric 9(11) : 13(18)- and 9(11) : 12-dienyl acetates by treatment with mineral acid (Beaton, Johnston, McKean, and Spring, *J.*, 1953, 3660; Allan, Johnston, and Spring, *J.*, 1954, 1546). A study of the stabilities of the three ursadien-3β-yl acetates has now been made. Treatment of ursa-9(11) : 13(18)-dien-3β-yl acetate (XII) with hydrochloric–acetic acid gives oleana-11 : 13(18)-dien-3β-yl acetate (VII) in 30% (crude) and 10% (pure) yield. The conversion of ursa-9(11) : 13(18)-dien-3β-yl acetate (XII) into oleana-11 : 13(18)-dien-3β-yl acetate proceeds through ursa-11 : 13(18)-dien-3β-yl acetate (IX) since the latter compound is obtained from (XII) under milder acid conditions, and treatment of (IX) with hydrochloric–acetic acid also gives oleana-11 : 13(18)-dienyl acetate (VII) in 10% (pure) yield. Again, the same treatment of the homoannular ursa-9(11) : 12-dien-3β-yl acetate (XI) gives oleana-11 : 13(18)-dien-3β-yl acetate (VII) in similar yield. The conversion of the three ursadien-3β-yl acetates into (VII) proves that the stereochemistry of α-amyrin is represented by the cipher (XIII); the configurations shown in (IX), (XI), and (XII) are consequential.



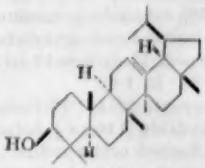
The ultraviolet absorption spectra of oleana- and ursa-11 : 13(18)-dien-3β-yl acetate show small differences which were of value in following the isomerisations described above There is a slight difference in the location of two of the three maxima [2440, 2510, and

2600 Å for ursa-11 : 13(18)-dien-3β-yl acetate and 2420, 2500, and 2600 Å for oleana-11 : 13(18)-dien-3β-yl acetate] but a more pronounced difference exists in the definition of one of the secondary maxima. Whereas in the spectrum of oleana-11 : 13(18)-dien-3β-yl acetate there is a well-defined minimum at 2560 Å, in that of ursa-11 : 13(18)-dien-3β-yl acetate, there is a shoulder and not a minimum at this wavelength.

In an earlier paper (Allan and Spring, *J.*, 1955, 2125) reasons have been given in support of the thesis that the hydrogen attached to $C_{(18)}$ in α-amyrin is β orientated and that, as in β-amyrin, rings D/E are *cis*-β fused. A comparison of the lactones derived from ursolic and oleanolic acid (and other reasons) led Corey and Ursprung (*loc. cit.*) to the same view. The proof, supplied above, that the $C_{(17)}$ attachment in the ursane group is β-orientated make these different reasons overwhelmingly compulsive. The stereochemistry of β-amyrin is therefore represented by (XIV).

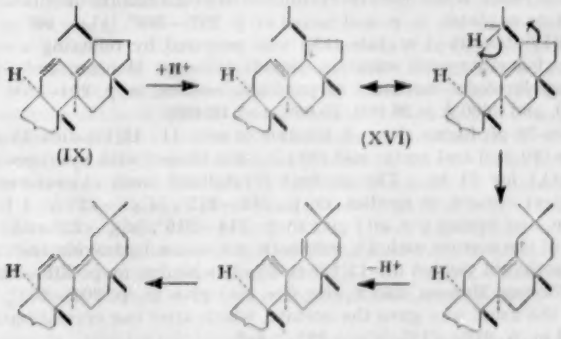


(XIV)



(XV)

We next turned to a consideration of the nature of ring E in α-amyrin. In ring E must repose the conformational and structural factors responsible for the stability of the *cis*-fusion of this ring with ring D. These factors must be responsible for the greater stability of urs-12-en-3β-yl acetate than that of urs-13(18)-en-3β-yl acetate, and also for a substantial hindering effect upon the double bond in α-amyrin and upon the ketone group in 12-oxoursan-3β-yl acetate. Again, ring E of the ursane group, although different from ring E of the oleanane group, must be so constituted that it can rearrange, under suitable conditions, to the latter. These factors and considerations are best reflected and explained, in our opinion, if ring E in α-amyrin is 5-membered with an *iso*propyl group attached to $C_{(19)}$. We therefore represent the constitution and stereochemistry of α-amyrin by (XV). The *iso*propyl group is given the β-configuration for two reasons. First, an α-*iso*propyl group gives a molecular structure in which there is severe interaction between this group and the $C_{(14)}$-methyl group. Secondly, the chosen configuration leads to a conformation in which the *iso*propyl



(IX) (XVI) (VII) (XVII)

group protects the double bond in α-amyrin and the carbonyl group in 12-oxoursan-3β-yl acetate, thus affording a satisfying explanation for the inert character of these two functional groups.

Ring E in α-amyrin has hitherto been represented as 6-membered with methyl groups attached to $C_{(19)}$ and $C_{(20)}$ (II). This representation depends upon reactions which include a

dehydrogenation. According to the formula (XV) for α-amyrin, these reactions involve rearrangement of ring E.

The acid-catalysed rearrangement of the ursadienyl acetates (XII) and (XI) probably includes, as a first phase, isomerisation to ursa-11 : 13(18)-dien-3β-yl acetate (IX), protonation of which gives the ion (XVI). The proximity of the $C_{(20)}$-hydrogen and C_{12}^{+} permits a transannular hydride exchange with synchronous ring enlargement, thus leading to the ion (XVII), the subsequent fate of which is depicted above.

Experimental

For general instructions see the preceding paper.

Attempted Isomerisation of 11-*Oxours*-12-*en*-3β-*yl Acetate* (IV).*—11-Oxours-12-en-3β-yl acetate (5 g.) in 15% ethanolic potassium hydroxide (400 c.c.) was heated under reflux for 50 hr. The product was isolated and acetylated in the usual way, and crystallised from chloroform–methanol, to refurnish 11-oxours-12-en-3β-yl acetate (4·5 g.) as plates, m. p. and mixed m. p. 283—286°, $[\alpha]_D$ +98° (*c*, 1·6).

3β : 11-*Diacetoxyursa*-9(11) : 12-*diene* (V).—A mixture of 11-oxours-12-en-3β-yl acetate (IX) (1·0 g.), acetic anhydride (140 c.c.), toluene-*p*-sulphonic acid (0·5 g.), and concentrated sulphuric acid (1 drop) was heated under reflux for 100 hr. The black solution was concentrated under reduced pressure on the steam-bath and diluted with water, and the product, a gum, isolated by means of ether. A solution of this in light petroleum was filtered through a short column of alumina. The filtrate was evaporated and the residue crystallised from chloroform–methanol, to give a first crop of plates, m. p. 275—283°, recrystallisation of which gave unchanged 11-oxours-12-en-3β-yl acetate (200 mg.), m. p. and mixed m. p. 287—288°, $[\alpha]_D$ +100° (*c*, 1·1). Concentration of the mother-liquors yielded prismatic rods, m. p. 203—206°, which after four recrystallisations from methanol gave 3β : 11-*diacetoxyursa*-9(11) : 12-*diene* as prisms (260 mg.), m. p. 213—214°, $[\alpha]_D$ +275° (*c*, 0·7), $\lambda_{max.}$ 2760 Å (ε 8000) (Found : C, 77·9; H, 9·9. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%).

Hydrolysis of 3β : 11-*Diacetoxyursa*-9(11) : 12-*diene* (V).—(*a*) A mixture of the enol acetate (50 mg.), methanol (50 c.c.), and concentrated hydrochloric acid (3 c.c.) was heated under reflux for 2 hr. Isolation of the product using ether, followed by acetylation by acetic anhydride and pyridine at 100°, gave 11-oxours-12-en-3β-yl acetate (36 mg.) as plates, m. p. and mixed m. p. 287—288°, $[\alpha]_D$ +98° (*c*, 1·0). (*b*) The enol acetate (100 mg.) in 3% aqueous-methanolic potassium hydroxide (50 c.c.) was heated under reflux for 1 hr. The product, isolated in the usual way, was acetylated by pyridine and acetic anhydride at 100°. Dilution of the mixture with water gave crystals, which were recrystallised from chloroform–methanol to yield 11-oxours-12-en-3β-yl acetate as plates, m. p. and mixed m. p. 287—288°, $[\alpha]_D$ +99° (*c*, 1·7).

Ursa-11 : 13(18)-dien-3β-yl acetate (IX) was prepared by refluxing a solution of α-amyrin acetate in benzyl acetate with selenium dioxide (Easton, Manson, and Spring, *loc. cit.*). It separated from chloroform–methanol as prismatic needles, m. p. 204—206°, $[\alpha]_D$ −76° (*c*, 1·0), $\lambda_{max.}$ 2440, 2510, and 2600 Å (ε 26,000, 29,000, and 18,400).

Urs-13(18)-*en*-3β-*yl Acetate* (X).—A solution of ursa-11 : 13(18)-dien-3β-yl acetate (400 mg.) in ethyl acetate (80 c.c.) and acetic acid (90 c.c.) was shaken with hydrogen and platinum (from 200 mg. of PtO_2) for 21 hr. The product crystallised from chloroform–methanol, to give urs-13(18)-en-3β-yl acetate as needles, m. p. 213—215°, $[\alpha]_D$ −22° (*c*, 1·1), ε 5500 at 2110 Å. Easton, Manson, and Spring (*loc. cit.*) give m. p. 214—216°, $[\alpha]_D$ −22° and ε 5100 at 2150 Å.

Hydrolysis of the acetate with 3% ethanolic potassium hydroxide and crystallisation of the product from methanol yielded urs-13(18)-en-3β-ol as blades, m. p. 201—202°, $[\alpha]_D$ −37°, −36° (*c*, 0·6, 1·1). Easton, Manson, and Spring (*loc. cit.*) give m. p. 204—205°, $[\alpha]_D$ −35°, −36·5°. Acetylation in the usual way gave the acetate, which after one crystallisation from methanol–chloroform had m. p. 210—212°, $[\alpha]_D$ −22° (*c*, 0·6).

Isomerisation of Urs-13(18)-*en*-3β-*yl Acetate to* α-*Amyrin Acetate.*—A solution of urs-13(18)-en-3β-yl acetate (150 mg.) in benzene (3 c.c.) and acetic acid (300 c.c.) was treated with concentrated sulphuric acid (5·7 c.c.), and the mixture heated at 80° for 5 min. and kept for 14 days at room temperature. The crystalline solid A (30 mg.) which had separated was collected. The filtrate was diluted with water, the mixture extracted with ether, and the extract washed in the

* This experiment was made by Dr. J. D. Easton, to whom we express our thanks.

usual way. Evaporation of the dried extract gave a gum, a solution of which in light petroleum–benzene (4 : 1) was chromatographed on alumina. Elution with the same solvent gave a crystalline fraction (53 mg.), which was combined with solid A, dissolved in light petroleum, and again chromatographed on alumina. Elution with light petroleum (150 c.c.) gave a crystalline fraction (35 mg.), which after two recrystallisations from chloroform–methanol yielded α-amyrin acetate as plates, m. p. 224—225°, $[\alpha]_D$ +78°. A mixture of this with an authentic sample, m. p. 226—227°, $[\alpha]_D$ +76° (*c*, 1·9), was undepressed in m. p.

Isomerisation of Ursa-9(11) : 13(18)-*dien*-3β-*yl Acetate* (XII) *to Ursa*-11 : 13(18)-*dien*-3β-*yl Acetate* (IX).—A solution of ursa-9(11) : 13(18)-dien-3β-yl acetate (105 mg.) in acetic acid (25 c.c.) and concentrated hydrochloric acid (1·0 c.c.) was heated on the steam-bath for 17 hr. Evaporation under reduced pressure gave a gum. A solution of this in chloroform–methanol deposited crystals, recrystallisation of which from the same solvent gave needles (35 mg.), m. p. 193—194°, ε 6900 at 2120 Å, $\lambda_{max.}$ 2440, 2500, and 2600 Å (ε 15,300, 16,300, and 10,800). This mixture in light petroleum (25 c.c.) was chromatographed on alumina (5 g.). Elution with light petroleum (100 c.c.) yielded mixtures. Continued elution with light petroleum (50 c.c.) furnished a fraction which crystallised from chloroform–methanol to give ursa-11 : 13(18)-dien-3β-yl acetate as needles (8 mg.), m. p. and mixed m. p. 203—204°, $[\alpha]_D$ −81° (*c*, 0·3), $\lambda_{max.}$ 2440, 2510, and 2600 Å (ε 26,800, 29,800, and 19,800).

Rearrangement of Ursa-9(11) : 13(18)-*dien*-3β-*yl Acetate* (XII) *to Oleana*-11 : 13(18)-*dien*-3β-*yl Acetate* (VII).—A solution of the 9(11) : 13(18)-dienyl acetate (500 mg.) in acetic acid (90 c.c.) and concentrated hydrochloric acid (7·5 c.c.) was heated on the steam-bath. After 4 hr. concentrated hydrochloric acid (2·5 c.c.) was added, and heating continued for 13 hr. The mixture was evaporated under reduced pressure, and the residue dissolved in light petroleum (100 c.c.) and chromatographed on alumina (25 g.). Elution with light petroleum (200 c.c.) gave a brown gum (269 mg.). Continued elution with light petroleum (600 c.c.) gave six fractions (145 mg.) which crystallised from chloroform–methanol as plates. These fractions ranged from m. p. 205—211°, $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 21,800, 25,000, 16,400), to m. p. 221—224°, $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 25,600, 29,000, and 18,500). They were combined and recrystallised from the same solvent to give oleana-11 : 13(18)-dien-3β-yl acetate (49 mg.) as hexagonal plates, m. p. and mixed m. p. 226—228°, $[\alpha]_D$ −63° (*c*, 1·0), $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 26,100, 28,700, and 19,100).

Rearrangement of Ursa-11 : 13(18)-*dien*-3β-*yl Acetate* (IX) *to Oleana*-11 : 13(18)-*dien*-3β-*yl Acetate* (VII).—A solution of ursa-11 : 13(18)-dien-3β-yl acetate (200 mg.) in acetic acid (70 c.c.) and concentrated hydrochloric acid (5 c.c.) was heated on the steam-bath for 17 hr. The mixture was evaporated under reduced pressure, and the residue dissolved in light petroleum (40 c.c.) and chromatographed on alumina (12 g.). Elution with light petroleum (300 c.c.) gave a gum (50 mg.). Further elution with light petroleum (400 c.c.) and light petroleum–benzene (20 : 1, 400 c.c.; 10 : 1, 250 c.c.) gave fractions (48 mg.) which crystallised from chloroform–methanol as plates, m. p. 219—222°. Recrystallisation of the combined fractions from the same solvent gave oleana-11 : 13(18)-dien-3β-yl acetate as plates (20 mg.), m. p. and mixed m. p. 225—226°, $[\alpha]_D$ −61° (*c*, 1·0), $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 23,500, 26,500, and 16,800).

Rearrangement of Ursa-9(11) : 12-*dien*-3β-*yl Acetate* (XI) *to Oleana*-11 : 13(18)-*dien*-3β-*yl Acetate* (VII).—A solution of the 9(11) : 12-dienyl acetate (1·0 g.) in acetic acid (180 c.c.) and concentrated hydrochloric acid (15 c.c.) was heated on the steam-bath for 2 hr. Concentrated hydrochloric acid (5 c.c.) was added, and heating continued for 17 hr. After evaporation under reduced pressure, the brown gum was dissolved in light petroleum (50 c.c.) and chromatographed on alumina (50 g.). Elution with light petroleum (600 c.c.) gave a gum (583 mg.). Further elution with light petroleum (1050 c.c.) gave fractions which crystallised from chloroform–methanol. These combined fractions recrystallised from chloroform–methanol, to give oleana-11 : 13(18)-dien-3β-yl acetate as hexagonal plates (82 mg.), m. p. and mixed m. p. 225—227°, $[\alpha]_D$ −64° (*c*, 0·9), $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 26,600, 30,000, and 19,300).

We thank the Carnegie Trust for the Universities of Scotland for a Scholarship (to J. M. B.).

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Triterpenoids. Part XL. The Characterisation of Alnusenone.*

By J. M. Beaton, F. S. Spring, and Robert Stevenson.

[Reprint Order No. 6220.]

A compound, $C_{30}H_{48}O$, isolated from black alder bark by Chapon and David (*Bull. Soc. chim. France*, **1953**, 333) has again been isolated from the same source. This compound, now named alnusenone, is shown to contain a reactive ketone group and one reactive double bond from which it follows that it is pentacyclic.

The isolation of an alcohol alnulin, and of a ketone protalnulin, from the barks of grey alder (*Alnus incana* L.) and black alder (*A. glutinosa* L.) was described by Zellner *et al.* (Zellner and Röglsperger, *Sitzungsber. Akad. Wiss. Wien*, 1923, **132**, 258; Zellner and Weiss, *ibid.*, 1925, **134**, 312; Fröschl and Zellner, *ibid.*, 1930, **139**, 476). Koller, Hiestand, Dietrich, and Jeger (*Helv. Chim. Acta*, 1950, **33**, 1050) showed that alnulin is identical with taraxerol, an alcohol isolated by Burrows and Simpson (*J.*, 1938, 2042) from the root of dandelion (*Taraxacum officinale*) and by Dunstan, Hughes, and Smithson (*Nature*, 1947, **160**, 577; *Austral. J. Chem.*, 1953, **6**, 321) from the bark of *Litsea dealbata* (*Lauraceae*), and that protalnulin is the related ketone, taraxerone. The constitution of taraxerol has recently been determined (Beaton, Spring, Stevenson, and Stewart, *J.*, 1955, 2131).

Extraction of black alder bark with light petroleum, followed by alkaline hydrolysis of the extract by the method of Koller *et al.* (*loc. cit.*), yielded a non-saponifiable fraction which was partly soluble in ether. A preliminary chromatography of the ether-insoluble fraction gave a mixture of ketones ($[\alpha]_D$ +28°). Crystallisation and chromatography of the mixture gave a homogeneous ketone, $C_{30}H_{48}O$, $[\alpha]_D$ +31°, which we name alnusenone, previously isolated from the same source by Chapon and David (*loc. cit.*). During an examination of two samples of the bark, Chapon and David found that one sample, collected in November, readily yielded taraxerol and taraxerone in agreement with the experience of Koller *et al.* (*loc. cit.*). The corresponding fraction from a second sample of bark, collected in February, consisted mainly of a compound $C_{30}H_{48}O$. A comparison of the constants of this and derived compounds described by these authors with alnusenone and its derivatives shows that the two are identical.

Later fractions obtained by us during the chromatographic separation of the ketone mixture had constants which approximate to those of taraxerone. The presence of taraxerone in the ketone mixture was established by reduction of the latter with lithium aluminium hydride, followed by acetylation, which gave a mixture of acetates from which taraxeryl acetate and alnusenyl acetate (see below) were easily separated.

The homogeneity of alnusenone was demonstrated by the following experiments. Reduction of the ketone with sodium and ethanol yields an alcohol, alnusenol, characterised as acetate, benzoate, and tribromoacetate. Hydrolysis of alnusenyl acetate refurnished alnusenol, oxidation of which by chromic acid at room temperature gave alnusenone; the physical constants of this preparation are identical with those of the ketone isolated from alder bark. Analyses of these derivatives, and particularly that of the tribromoacetate, agree with the molecular formula $C_{30}H_{48}O$ for alnusenone.

Alnusenone contains a reactive carbonyl group, since it readily forms an oxime. It also contains one ethylenic bond because alnusenyl acetate absorbs one mol. of hydrogen when reduced over platinum, yielding alnusanyl acetate. The carbonyl group and the double bond of alnusenone are not conjugated since its ultraviolet spectrum shows absorption only in the ethylenic region together with a weak band in the carbonyl region. The intensity of absorption in the ethylenic region suggests that the double bond is trisubstituted.

In contrast with alnusenyl acetate, alnusanyl acetate does not give a colour with tetranitromethane and does not show ethylenic ultraviolet absorption. Hydrolysis of

* Part XXXIX, preceding paper.

alnusanyl acetate yields alnusanol, oxidised by chromic acid at room temperature to alnusanone. That alnusanone (and, consequently, the parent alnusenone) is a ketone, and not an aldehyde, is established by its stability to chromic acid in acetic acid at room temperature and also by its infrared absorption spectrum (in Nujol) which includes a band at 1702 cm.$^{-1}$ typical of a 6-ring ketone. The infrared absorption spectrum of alnusenone also contains a carbonyl band at 1702 cm.$^{-1}$ (Nujol). Wolff–Kishner reduction of alnusenone gives an unsaturated hydrocarbon, alnusene, $C_{30}H_{50}$, catalytic hydrogenation of which yielded alnusane, also obtained by Wolff–Kishner reduction of alnusanone.

Although we cannot give a direct proof that alnusenone is triterpenoid, its molecular formula and its close association with taraxerone justify its provisional inclusion in this group. If our assessment of the molecular formula of alnusenone is correct, its characterisation as a monoethenoid ketone shows that it is pentacyclic. The physical constants of alnusene (m. p. 181—181·5°, $[\alpha]_D$ +56°, +58°) are similar to those of ψ-taraxastene (heterolupene) (m. p. 182—184°, $[\alpha]_D$ +50°; Jeger, Krüsi, and Ruzicka, *Helv. Chim. Acta*, **1947**, **30**, 1048; Ames, Beton, Bowers, Halsall, and Jones, *J.*, 1954, 1905). The two hydrocarbons differ, however, because the physical constants of taraxastane (Jeger, Krüsi, and Ruzicka, *loc. cit.*) are different from those of alnusane. The constants of alnusane (m. p. 235—236°, $[\alpha]_D$ +27°) are similar to those of lupane-I (m. p. 231—233°, $[\alpha]_D$ +22°; Ames *et al.*, *loc. cit.*); the two hydrocarbons are distinct since a mixture showed a large m. p. depression. We thank Professor E. R. H. Jones, F.R.S., for the sample of lupane-I.

	$[M]_D$						
	Alcohol	Acetate	Benzoate	Ketone	Δ_1	Δ_2	Δ_3
Alnusenol	+260°	+216°	+88°	+132°	−44°	−172°	−128°
Alnusanol	+125°	+ 63°	—	+222°	−62°	—	+ 97°

The constants of alnusane are also similar to those of friedelane. A specimen of the last hydrocarbon was prepared from friedelin by the Wolff–Kishner method and in agreement with Bruun (*Acta Chem. Scand.*, **1954**, **8**, 71, 76) friedelane had m. p. 248—250°, $[\alpha]_D$ +22° (*c*, 0·6). Alnusane and friedelane are distinct hydrocarbons since a mixture showed a large depression in m. p.

Alnusenone gives a negative reaction in the Zimmermann test, and in this respect it differs from taraxer-14-en-3-one (taraxerone) and from other 3-oxo-derivatives of the pentacyclic triterpenoids (Barton and de Mayo, *J.*, 1954, 887). The differences between the molecular rotations of alnusenol derivatives (see above) show some striking deviations from those between corresponding derivatives of known 3-hydroxy-triterpenoids.

Experimental

For general instructions see Part XXXVIII (*J.*, 1955, 2606).

Alnusenone from Black Alder Bark.—Finely powdered bark was extracted with light petroleum, and the extracted matter hydrolysed as described by Koller *et al.* (*loc. cit.*). A preliminary chromatography of the ether-insoluble non-saponifiable fraction yielded a solid (eluted by light petroleum–benzene and by benzene) which separated from chloroform–methanol as plates, m. p. 235—237°, $[\alpha]_D$ +28° (*c*, 2·0). This solid (11·5 g.) was crystallised once from light petroleum and twice from benzene (mother-liquors A) to give long blades (1·9 g.), m. p. 241—243°, $[\alpha]_D$ +31° (*c*, 2·0), a solution of which in light petroleum–benzene (20 : 1; 1 l.) was chromatographed on alumina (150 g.). Elution with the same solvent mixture (6 l.) gave fractions of m. p.s 245—246° and $[\alpha]_D$ +31° to +30° (*c*, 1·8—2·0). These fractions were combined and crystallised from benzene to give alnusenone as large thick blades (1·5 g.), m. p. 245—246°, $[\alpha]_D$ +31° (*c*, 2·1), $\lambda_{max.}$ 2950 Å (ε 61), ε 3900 at 2050 Å (Chapon and David, *loc. cit.*, give m. p. 247°, $[\alpha]_D$ +31°) (Found: C, 84·7, 85·1; H, 11·6, 11·4. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%). The *oxime* separates from ethyl acetate as needles, m. p. 288—290° (decomp.) (Found: C, 82·1; H, 11·0; N, 3·4. $C_{30}H_{49}ON$ requires C, 81·9; H, 11·2; N, 3·2%).

The mother-liquors A were evaporated and the solid chromatographed on alumina. Earlier fractions from the chromatogram furnished pure alnusenone (*ca.* 1·3 g.), m. p. 245—246°, $[\alpha]_D$ +31·5° (*c*, 1·8). The specific rotation of subsequent fractions diminished progressively, the final fractions giving slightly impure taraxerone, m. p. 237—240°, $[\alpha]_D$ +14° (*c*, 2·2).

Alnusenyl Acetate.—(*a*) A solution of alnusenone (150 mg.) in benzene (3 c.c.) and ethano (15 c.c.) was treated, during 5 min., with sodium (1·0 g.), and the mixture refluxed for 1 hr. The product was isolated in the usual way and acetylated by acetic anhydride and pyridine at 90°. The acetylated product, crystallised from chloroform–methanol, furnished alnusenyl acetate as needles, m. p. 235—236°, $[\alpha]_D$ +46° (*c*, 1·0), ε 4500 at 2070 Å (Chapon and David give m. p. 235—236°, $[\alpha]_D$ +41·5°) (Found: C, 81·9; H, 11·2. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). It gives a yellow colour with tetranitromethane.

(*b*) The ketone mixture described above (1·85 g.; m. p. 235—237°, $[\alpha]_D$ +28°) in dry ether (500 c.c.) was refluxed for 2 hr. with lithium aluminium hydride (2·5 g.). The product was acetylated and then crystallised as in (*a*), giving a first crop (mother-liquor B) of plates (280 mg.), m. p. 302—305°, $[\alpha]_D$ +11·5° (*c*, 0·6), recrystallisation of which from the same solvent gave taraxeryl acetate, m. p. 303—305°, $[\alpha]_D$ +12° (*c*, 1·1) (Found: C, 81·6; H, 11·35. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Alkaline hydrolysis of the acetate gave taraxerol, separating as small plates (from chloroform–methanol), m. p. 284—286°, $[\alpha]_D$ ±0° (*c*, 0·5), oxidation of which by chromic acid in acetic acid at room temperature gave taraxerone as prismatic plates (from chloroform–methanol), m. p. 242—244°, $[\alpha]_D$ +9°, +9·5° (*c*, 1·3, 1·4). Koller *et al.* (*loc. cit.*) give m. p. 304—305°, $[\alpha]_D$ +9°, m. p. 282—283°, $[\alpha]_D$ ±0°, and m. p. 240—241°, $[\alpha]_D$ +11°, for taraxeryl acetate, taraxerol, and taraxerone respectively.

Evaporation of the mother-liquor B and crystallisation of the residue from chloroform–methanol gave alnusenyl acetate (910 mg.) as needles, m. p. and mixed m. p. 235—237°, $[\alpha]_D$ +46°, +47° (*c*, 1·0, 1·1).

Alnusenol.—A solution of alnusenyl acetate (600 mg.; m. p. 235—237°) in 3% ethanolic potassium hydroxide was refluxed for 3 hr. Crystallisation of the product from methanol gave alnusenol as fine needles, m. p. 203—205°, $[\alpha]_D$ +61° (*c*, 0·9, 1·0) (Chapon and David give m. p. 195—196°, $[\alpha]_D$ +59·5° for this compound) (Found: C, 84·3; H, 12·1. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). Dr. S. David has kindly supplied us with a sample of this alcohol, m. p. 193·5—194·5°, $[\alpha]_D$ +60°. In our apparatus, this has m. p. 198—199°, and a mixture with alnusenol, m. p. 200—202°, $[\alpha]_D$ +61°, had m. p. 199—201°.

Alnusenol (200 mg.), in benzene (10 c.c.) and glacial acetic acid (50 c.c.), was treated at room temperature with a solution of chromium trioxide (34·4 mg.) in glacial acetic acid (6·9 c.c.), added dropwise during 10 min. After 1 hr. at room temperature, the product was isolated in the usual way and crystallised from chloroform–methanol to yield alnusenone as plates, m. p. and mixed m. p. 245—247°, $[\alpha]_D$ +31° (*c*, 1·0) (Found: C, 84·8; H, 11·65%).

Alnusenyl benzoate separates from chloroform–methanol as needles, m. p. 234—235°, $[\alpha]_D$ +16·5° (*c*, 1·0) (Chapon and David, *loc. cit.*, give m. p. 234°, $[\alpha]_D$ +10·7°) (Found; C, 83·9; H, 10·5. Calc. for $C_{37}H_{54}O_2$: C, 83·7; H, 10·5%).

A solution of alnusenol (135 mg.) in benzene (15 c.c.) and pyridine (10 c.c.) at 0° was treated dropwise during 3 min. with a solution of tribromoacetyl bromide (0·5 c.c.) in benzene (5 c.c.). The mixture was kept at 0—5° for 30 min., then at room temperature for 2 days. The filtered solution was treated in the usual manner and the product crystallised from ether–acetone to give *alnusenyl tribromoacetate* as needles, m. p. 223° (decomp.), $[\alpha]_D$ +26° (*c*, 1·2) (Found: C, 54·7; H, 7·2. $C_{32}H_{49}O_2Br_3$ requires C, 54·5; H, 7·0%).

Alnusene.—A mixture of alnusenone (300 mg.), sodium methoxide solution (from 1 g. of sodium and 25 c.c. of methanol), and 100% hydrazine hydrate (3 c.c.) was kept at 205° for 18 hr. (autoclave). The product was purified by chromatography on alumina to give *alnusene* (128 mg.); it separated from chloroform–methanol as elongated plates, m. p. 181—181·5°, $[\alpha]_D$ +56° (*c*, 1·8) (Found: C, 87·4; H, 12·2. $C_{30}H_{50}$ requires C, 87·7; H, 12·3%). It gives a yellow colour with tetranitromethane.

Alnusanyl Acetate.—A solution of alnusenyl acetate (200 mg.) in glacial acetic acid (200 c.c.) was shaken with platinum (from 150 mg. of PtO_2) and hydrogen for 3 hr., hydrogen absorption (*ca.* 1 mol.) then being complete. The product crystallised from chloroform–methanol to yield *alnusanyl acetate* as plates, m. p. 264—265°, $[\alpha]_D$ +11°, +11·5° (*c*, 1·6, 1·7) (Found: C, 81·4; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%). Alnusanyl acetate was recovered unchanged after treatment of its solution in chloroform at room temperature with a stream of dry hydrogen chloride for 1 hr.

Alnusanol, obtained from the acetate by using 3% methanolic potassium hydroxide, crystallised from chloroform–methanol as fine needles, m. p. 255—256°, $[\alpha]_D$ +28° (*c*, 0·8), unchanged on further recrystallisation (Found: C, 82·3, 82·8; H, 12·25, 12·4. $C_{30}H_{52}O,\frac{1}{2}CH_3{\cdot}OH$ requires C, 82·4; H, 12·25%).

Alnusanone.—Alnusanol (400 mg.), in benzene (100 c.c.) and glacial acetic acid (200 c.c.),

was treated at room temperature with a solution of chromium trioxide (68·4 mg.) in glacial acetic acid (13·7 c.c.), added dropwise during 20 min. After 75 min., the solvent was removed under reduced pressure and the neutral product, isolated in the usual manner, chromatographed in light petroleum (150 c.c.) on alumina (12 g.). Elution with light petroleum (150 c.c.) gave an amorphous solid (44 mg.). Continued washing with light petroleum (400 c.c.) and light petroleum–benzene (1 : 1; 50 c.c.) gave fractions (259 mg.) which crystallised from chloroform–methanol as flattened needles (170 mg.), m. p. 227—230°, $[\alpha]_D$ +51° (*c*, 1·7). Four recrystallisations from the same solvent gave *alnusanone*, m. p. 228—230°, $[\alpha]_D$ +52° (*c*, 1·7) (Found: C, 84·0; H, 11·8. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Further elution of the column with ether (50 c.c.) gave alnusanol (65 mg.), m. p. and mixed m. p. 254—256°. Alnusanone gives a negative reaction in the Zimmermann test.

Alnusane.—(*a*) Alnusanone (80 mg.), sodium methoxide solution (from 0·5 g. of sodium and 25 c.c. of methanol), and 100% hydrazine hydrate (2 c.c.) were heated in an autoclave at 200° for 22 hr. The product, isolated by means of ether, crystallised from chloroform–methanol as small plates (28 mg.), m. p. 234—236°, $[\alpha]_D$ +30° (*c*, 0·8). Recrystallisation from the same solvent gave *alnusane* as plates, m. p. 235—236°, $[\alpha]_D$ +27° (*c*, 1·6) (Found: C, 87·6; H, 13·1. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%). It does not give a colour with tetranitromethane.

(*b*) A solution of alnusene (65 mg.) in glacial acetic acid (200 c.c.) was shaken with platinum (from 100 mg. of PtO_2) and hydrogen for 1 hr. The product, part of which separated during the reaction, was isolated in the usual manner and crystallised from chloroform–methanol to give alnusane as plates (53 mg.), m. p. and mixed m. p. 234—236°, $[\alpha]_D$ +24° (*c*, 1·5).

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Experiments concerning the Structure of a Constituent of Orcein.

By J. F. W. McOMIE and I. M. WHITE.

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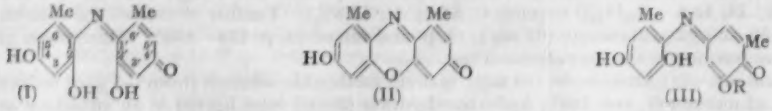
Condensation of 6-methoxy-*p*-toluquinone 4-chloroimide with orcinol in alkaline solution gives evidence for the formation of the sterically hindered indophenol (III; R = Me). The instability of the latter together with the failure of the appropriate reaction to yield the trihydric phenol (III; R = H) make it unlikely that the compound isolated by Liebermann from orcein possesses the structure (III; R = H) and even less likely that it has the more hindered structure (I) which was suggested by Henrich.

LIEBERMANN (*Ber.*, 1875, **8**, 1649) isolated two purple compounds from the mixture obtained by the action of air and ammonia on orcinol, one of the methods used commercially for the preparation of the purple dye orcein. Henrich (*Sitzungsber. physik.-med. Soc. Erlangen*, 1939, **71**, 199; *Chem. Zentr.*, 1940, **I**, 858) suggested that one of the compounds ($C_{14}H_{13}O_4N$) was 2 : 2′-dihydroxy-6 : 6′-dimethylindophenol (I), but it has not been possible to consult Henrich's paper, and structure (I) appears unlikely. Scale drawings reveal a large amount of steric hindrance which would prevent the molecule from being planar and hence would lessen its stability. The steric hindrance could be relieved by loss of a molecule of water to give the known dye orcirufin (II), and indeed, the latter is actually formed by the condensation of 2-nitroso-orcinol with orcinol in concentrated sulphuric acid instead of the "expected" indophenol (I) (Nietzki and Mackler, *Ber.*, 1890, **23**, 722).

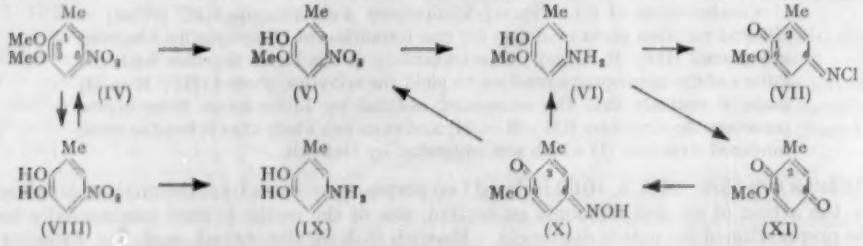
It seemed possible that 2 : 3′-dihydroxy-5′ : 6-dimethylindophenol (III; R = H), isomeric with the indophenol (I), might be formed from orcinol by amination followed by coupling with another molecule of orcinol and introduction of the fourth oxygen atom by aerial oxidation. The indophenol (III) is somewhat sterically hindered, but much less so than its isomer (I). The closely related dye, 2 : 6 : *N* : *N*-tetramethylindoaniline, was

prepared by Vittum and Brown (*J. Amer. Chem. Soc.*, 1947, **69**, 152) and, in contrast to Liebermann's compound, it was rapidly decomposed by water. Despite the expected instability of the indophenol (III; R = H), attempts were made to synthesise it together with its mono- and di-methyl ethers and some related indophenols because (*a*) if it could be made it might be identical with Liebermann's compound, and (*b*) if it could not be made by the usual methods, this would be evidence for its instability and at the same time further evidence against the existence of the much more hindered indophenol (I).



2-Hydroxy-3-methoxy-5-nitrotoluene (V) was made by the partial demethylation of 2 : 3-dimethoxy-5-nitrotoluene (IV). Its structure was proved by reduction to the amine (VI) followed by oxidation to the known 6-methoxy-*p*-toluquinone (XI). The required nitrophenol was also obtained by the oxidation of 6-methoxy-*p*-toluquinone 4-mono-oxime (X), but it could not be prepared by direct nitration of 2-hydroxy-3-methoxytoluene; instead, this reaction gave 3 : 3′-dimethoxy-5 : 5′-dimethyl-4 : 4′-diphenoquinone (cf. below).

Reduction of the nitrophenol (V) with sodium dithionite gave the unstable 5-amino-2-hydroxy-3-methoxytoluene (VI), best isolated as its hydrochloride. The overall yield of the aminophenol (VI) by this route (IV ⟶ V ⟶ VI) was poor. A better method involved coupling 2-hydroxy-3-methoxytoluene with diazotised sulphanilic acid and reducing the azo-dye with stannous chloride. The best method, however, was the reduction of the mono-oxime (X), which is conveniently prepared by nitrosation of 2-hydroxy-3-methoxytoluene with pentyl nitrite and sodium ethoxide. The same mono-oxime (X) was obtained in poor yield by the action of hydroxylamine on 6-methoxy-*p*-toluquinone (XI). During an attempt to prepare the mono-oxime (X) by the action of hydroxylamine and hydrogen peroxide on 2-hydroxy-3-methoxytoluene (cf. Wurster, *Ber.*, 1887, **20**, 2632) a colourless compound was isolated. The same compound was also formed in the absence of hydroxylamine and was shown to be 4 : 4′-dihydroxy-3 : 3′-dimethoxy-5 : 5′-dimethyldiphenyl which had previously been prepared by Majima and Takayama (*ibid.*, 1920, **53**,



1913) by reduction of the corresponding diphenoquinone, itself prepared by oxidation of 2-hydroxy-3-methoxytoluene by ferric chloride. Similarly, we obtained the diphenoquinone by the action of nitrous acid on 2-hydroxy-3-methoxytoluene.

5-Amino-2-hydroxy-3-methoxytoluene (VI) was smoothly converted into 6-methoxy-*p*-toluquinone 4-chloroimide (VII) by the action of sodium hypochlorite. Complete demethylation of 2 : 3-dimethoxy-5-nitrotoluene (IV) was effected by boiling with hydrobromic acid in acetic acid. The resulting 2 : 3-dihydroxy-5-nitrotoluene (VIII) was reduced to the very unstable amine (IX) which could not be converted into the desired 6-hydroxy-*p*-toluquinone 4-chloroimide.

Condensation of the chloroimide (VII) with orcinol in presence of alkali gave a deep blue solution of the sodium salt of 2-hydroxy-3′-methoxy-5′ : 6-dimethylindophenol (III; R = Me), but the compound decomposed in a few hours and no pure product could be isolated. Similar results were obtained when the same chloroimide was condensed with

resorcinol and with phloroglucinol dimethyl ether. On the other hand, the following condensations under appropriate conditions failed to yield indophenols: 2-nitroso-orcinol with 3-methylcatechol to give the indophenol (III; R = H); 6-methoxy-*p*-toluquinone 4-mono-oxime (X) or the chloroimide (VII) with orcinol monomethyl ether to give the dimethyl ether of the indophenol (III; R = H).

Some preliminary experiments were carried out with the readily available 2 : 6-dichloro-*p*-benzoquinone 4-chloroimide (Apte and Panse, *J. Indian Chem. Soc.*, 1947, **24**, 375). Condensation with resorcinol gave a purple solution, but decomposition occurred before any product could be isolated. Reaction with resorcinol monomethyl ether was smooth, but analysis of the product showed that the empirical formula was $C_{13}H_8O_3NCl_2{\cdot}OMe$ instead of $C_{12}H_6O_2NCl_2{\cdot}OMe$ for the expected 3 : 5-dichloro-2′-methoxyindophenol. The compound is possibly a hydroxymethyl derivative of the expected indophenol.

The failure of the appropriate reactions to yield 2 : 3′-dihydroxy-5′ : 6-dimethylindophenol (III; R = H) or its dimethyl ether, together with the instability of the monomethyl ether (III; R = Me) are strong indications that Liebermann's compound does not possess the indophenol structure (III; R = H) and renders Henrich's suggested structure (I) even less likely. We now consider that the purple colour and stability of Liebermann's compound are in better accord with an oxazine type of structure.

Experimental

2 : 3-*Dimethoxy-5-nitrotoluene* (IV).—2 : 3-Dimethoxytoluene (b. p. 95—96°/19 mm.) was made in 93% yield by methylation of 2 : 3-dihydroxytoluene and was nitrated in 55% yield by a modification of Majima and Okazaki's method (*Ber.*, 1916, **49**, 1482).

2-*Hydroxy-3-methoxy-5-nitrotoluene* (V).—(a) *From* 2 : 3-*dimethoxy-5-nitrotoluene* (IV). Potassium hydroxide (16 g.) was added cautiously to 2 : 3-dimethoxy-5-nitrotoluene (IV) (10 g.) in hot 50% aqueous ethanol (150 ml.). The mixture was boiled under reflux for 23 hr., then set aside for 2 days. After filtration, the solution was distilled through a short fractionating column until 70—80 ml. of distillate had been collected. The cooled solution was extracted with a large volume of ether to remove unchanged material, then acidified, and the brown needles were collected. Recrystallisation from aqueous ethanol (charcoal) gave 2-*hydroxy*-3-*methoxy-5-nitrotoluene* (1·4 g.), m. p. 104—107°. Two more recrystallisations gave almost colourless needles (1·1 g., 12%), m. p. 106—108° (Found: C, 52·8; H, 5·0; N, 7·8. $C_8H_9O_4N$ requires C, 52·5; H, 5·0; N, 7·7%). The compound is readily soluble in ethanol and benzene, less readily in light petroleum, and sparingly soluble in water. It gives a bright red colour in aqueous alkali, but no colour with ferric chloride. 2-*Acetoxy*-3-*methoxy-5-nitrotoluene*, thrice crystallised from aqueous ethanol, formed pale yellow needles, m. p. 98—99° (Found: C, 53·1; H, 5·1; N, 6·0. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9; N, 6·2%).

(b) *From* 6-*methoxy*-p-*toluquinone* 4-*mono-oxime* (X). A hot solution of potassium ferricyanide (4·0 g.) in 2N-sodium hydroxide (10 ml.) was added to a boiling solution of 5-methoxy-*p*-toluquinone 4-mono-oxime (2-hydroxy-3-methoxy-5-nitrosotoluene) (0·5 g.) in 2N-sodium hydroxide (5 ml.), and the mixture heated on a steam-bath for 2½ hr. The cold solution was filtered, acidified, and extracted with ether. The ethereal solution was washed with dilute aqueous sodium hydroxide, then the aqueous solution was acidified and the nitro-phenol collected. Recrystallisation from water (charcoal) gave silky needles, m. p. 107—108°, undepressed when mixed with the nitro-phenol (V) prepared as above.

5-*Amino*-2-*hydroxy*-3-*methoxytoluene* (VI).—(a) *From* 2-*hydroxy*-3-*methoxy-5-nitrotoluene* (V). Sodium dithionite (hydrosulphite) (*ca.* 5 g.) was added gradually to 2-hydroxy-3-methoxy-5-nitrotoluene (V) (1·0 g.) in 10% sodium hydroxide (40 ml.) at 70—80° until the deep red colour was discharged. The cold solution was acidified with acetic acid, and the 5-amino-2-hydroxy-3-methoxytoluene [needles, m. p. 128—130° (decomp.)] was collected. It was dissolved in dilute hydrochloric acid containing a little stannous chloride, and treated with charcoal, and the solution concentrated. The *amine hydrochloride* separated as almost colourless prisms, decomp. between 230° and 250° (Found: C, 50·4; H, 6·5; N, 7·3; Cl, 18·1. $C_8H_{12}O_2NCl$ requires C, 50·7; H, 6·4; N, 7·4; Cl, 18·7%). 5-*Acetamido*-2-*acetoxy*-3-*methoxytoluene*, recrystallised from water, then twice from benzene–light petroleum (b. p. 60—80°), formed plates, m. p. 157—158° (Found: C, 61·1; H, 6·3; N, 5·7. $C_{12}H_{15}O_4N$ requires C, 60·7; H, 6·4; N, 5·9%).

(b) *By reduction of* 6-*methoxy*-p-*toluquinone* 4-*mono-oxime* (X). The powdered mono-oxime (4·9 g.) was added in small portions to a hot solution of stannous chloride (18 g.) in concentrated

hydrochloric acid (55 ml.). Heating on the steam-bath was continued for 20 min. When cool, the crystals were collected and dissolved in water (150 ml.). The tin salts were removed by precipitation with hydrogen sulphide. After filtration, concentrated hydrochloric acid (20 ml.) and a little stannous chloride were added. Concentration of the solution gave 5-amino-2-hydroxy-3-methoxytoluene hydrochloride as almost colourless prisms (4·6 g., 85%). The pure hydrochloride is comparatively stable. A sample kept for 3 years was dark, but was only slightly impure.

(c) *From 2-hydroxy-3-methoxytoluene.* 2-Hydroxy-3-methoxytoluene (4·6 g.) (Cosgrove and Waters, *J.*, 1949, 3193) was coupled with diazotised sulphanilic acid, and the resulting azo-dye reduced by stannous chloride in the usual way. The amine hydrochloride obtained (1·0 g., 16%) gave a diacetate identical (mixed m. p.) with that prepared in two steps from the nitro-compound and from the oxime in (a) and (b) above.

Oxidation of 5-Amino-2-hydroxy-3-methoxytoluene (VI).—Hydrated ferric sulphate (5·0 g.) was added carefully (frothing) to 5-amino-2-hydroxy-3-methoxytoluene hydrochloride (0·5 g.) in water (40 ml.) containing sodium hydrogen carbonate (0·25 g.). Steam was then blown through the mixture until the distillate was no longer yellow. The 6-methoxytoluquinone (XI) was collected from the distillate by extraction with ether, and recrystallised from light petroleum (b. p. 60—80°), being thereby obtained as fluffy yellow needles, m. p. 148—150°, undepressed by admixture with an authentic sample made by the oxidation of orcinol dimethyl ether (Asahina and Fuzikawa, *Ber.*, 1934, **67**, 167).

6-*Methoxy*-p-*toluquinone* 4-*Chloroimide* (VII).—Chlorine (40—50 g.) was absorbed in sodium hydroxide (35 g.) in water (50 ml.) and ice (500 g.). The sodium hypochlorite thus prepared was added gradually, with stirring, to the hydrochloride of the amine (VI) (5 g.) in water (200 ml.) and ice (80 g.) at 0° until the orange colour was just discharged. The canary-yellow precipitate (4·5 g.) was collected and recrystallised from ethanol, giving the *chloroimide* (VII) as orange-yellow needles or plates (3·2 g., 65%), m. p. 131—133° (decomp.), raised to 140—142° (decomp.) by recrystallisation from light petroleum (b. p. 60—80°) (charcoal) (Found: C, 52·2; H, 4·3; N, 7·4; Cl, 19·9. $C_8H_8O_2NCl$ requires C, 51·8; H, 4·3; N, 7·5; Cl, 19·1%).

6-*Methoxy*-p-*toluquinone* 4-*Mono-oxime* (X).—(a) *From 2-hydroxy-3-methoxytoluene.* Freshly distilled pentyl nitrite (3·8 g.) was added to a solution of 2-hydroxy-3-methoxy toluene (4·1 g.) in ethanolic sodium ethoxide (0·9 g. of sodium in 44 ml. of ethanol). After 3 days, the solution was diluted with water (150 ml.) and filtered. The filtrate was acidified rapidly at 0° with dilute sulphuric acid. After several hours the emulsion yielded orange-brown prisms (3·2 g.). If the emulsion is agitated, a less pure product is obtained. Recrystallisation from acetone–light petroleum (b. p. 60—80°) gave the *mono-oxime* (X) as pale orange prisms (2·6 g., 53%). After two more recrystallisations, this had m. p. 195—198° (decomp.; sintering from 185°) (Found: C, 57·5; H, 5·4; N, 8·5. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%).

(b) *From 6-methoxy*-p-*toluquinone* (XI). A solution of hydroxylamine hydrochloride (0·35 g.) in water (7 ml.), adjusted to pH 6—7, was added with shaking to a solution of 6-methoxy-*p*-toluquinone (XI) (0·5 g.) in chloroform (10 ml.) and ethanol (25 ml.). Next day the mixture was concentrated to a few ml., diluted with water, and then extracted with chloroform, yielding a dark solid. After 3 recrystallisations from chloroform–benzene (charcoal) and shaking of the solution with silica gel in the third crystallisation, the product was obtained as orange prisms. Three recrystallisations from acetone–light petroleum (b. p. 60—80°) gave the pure mono-oxime (X), m. p. *ca.* 203—205° (decomp.) (Found: C, 57·4; H, 5·4; N, 8·5%).

The products from (a) and (b) were shown to be identical by the similarity of their *X*-ray powder photographs and of their crystal form.

Oxidation of 2-Hydroxy-3-methoxytoluene.—(a) *With nitric acid.* A mixture of concentrated nitric acid (1·6 ml.) and glacial acetic acid (3·5 ml.) was added dropwise with vigorous stirring to 2-hydroxy-3-methoxytoluene (2·4 g.) in glacial acetic acid (50 ml.), the temperature rising to *ca.* 40°. After 1½ hr., 3 : 3′-dimethoxy-5 : 5′-dimethyl-4 : 4′-diphenoquinone (0·9 g.) was filtered off. A portion thrice recrystallised from acetone had m. p. 203° (decomp.) (Found: C, 70·2; H, 5·6. Calc. for $C_{16}H_{16}O_4$: C, 70·6; H, 5·9%).

Crude diphenoquinone (0·9 g.) was reduced by sodium dithionite (hydrosulphite) and then methylated by methyl sulphate and potassium hydroxide, thereby yielding 3 : 3′-4 : 4′-tetramethoxy-5 : 5′-dimethyldiphenyl (0·6 g.) as leaflets, m. p. 110—111°, after one recrystallisation from aqueous ethanol [Found: C, 71·4; H, 7·3; OMe, 41·0. Calc. for $C_{14}H_{10}(OMe)_4$: C, 71·5; H, 7·3; OMe, 41·0%].

Majima and Takayama (*Ber.*, 1920, **53**, 1913) record m. p. 202—203° and 102—103° for the diphenoquinone and the tetramethoxydiphenyl respectively.

(b) *With hydrogen peroxide.* A mixture of 2-hydroxy-3-methoxytoluene (4 g.), ethanol (35 ml.), and hydrogen peroxide (40 ml.; 90—100-vol.) was boiled for 2½ hr. under reflux. After steam-distillation to remove ethanol and unchanged phenol, the solution was cooled and the solid collected. Recrystallisation from methanol gave 4 : 4′-dihydroxy-3 : 3′-dimethoxy-5 : 5′-dimethyldiphenyl as needles (0·4 g.), m. p. 185—186°, raised to 188° by another recrystallisation (Majima and Takayama, *loc. cit.*, record m. p. 189°). Methylation by methyl sulphate and sodium hydroxide gave 3 : 3′ : 4 : 4′-tetramethoxy-5 : 5′-dimethyldiphenyl, m. p. and mixed m. p. 109—111°.

(c) *With nitrous acid.* Dilute sulphuric acid (4·1 g. of acid of *d* 1·84 in 30 ml. of water) was added slowly to a stirred solution at 0° of 2-hydroxy-3-methoxytoluene (1·6 g.), potassium hydroxide (1·0 g.), and sodium nitrite (2·1 g.) in water (50 ml.). After 1 hr. the product was collected by filtration and recrystallised from acetone, giving 3 : 3′-dimethoxy-5 : 5′-dimethyl-4 : 4′-diphenoquinone as dark violet needles, m. p. and mixed m. p. 200—203° (decomp.).

2 : 3-*Dihydroxy-5-nitrotoluene* (VIII).—A mixture of 2 : 3-dimethoxy-5-nitrotoluene (IV) (7·5 g.), 60% aqueous hydrobromic acid (60 ml.), and acetic acid (40 ml.) was boiled under reflux for 2 hr. More hydrobromic acid (40 ml.) was added and the boiling continued for another 3 hr. The cooled mixture was diluted with water (400 ml.) and neutralised with solid sodium hydrogen carbonate, then the product was collected in ether. After removal of the solvent, the residue was dissolved in water, and lead acetate solution added until precipitation of the bright red lead salt was complete. The latter was suspended in water (250 ml.), and dilute sulphuric acid added with vigorous stirring. After filtration the solution was concentrated (charcoal), and cooled, yielding bright yellow crystals of 2 : 3-*dihydroxy-5-nitrotoluene* (3·0 g.), m. p. 134—135°, raised to 138° by three recrystallisations from water (Found: C, 47·0; H, 4·6; N, 8·2. $C_7H_7O_4N,\frac{1}{2}H_2O$ requires C, 47·2; H, 4·5; N, 7·9%). The compound is apparently a trihydrate which is converted into the hemihydrate on drying at 100° under reduced pressure (loss in wt., 18·2; theor., 20·2%). It gives a deep blood-red colour in aqueous alkali. Methylation of the nitro-compound regenerated 2 : 3-dimethoxy-5-nitrotoluene. Acetylation gave 2 : 3-*diacetoxy-5-nitrotoluene*, m. p. 114—115° (Found: C, 52·1; H, 4·2; N, 5·4. $C_{11}H_{11}O_6N$ requires C, 52·2; H, 4·3; N, 5·5%).

5-*Amino*-2 : 3-*dihydroxytoluene* (IX).—Finely powdered 2 : 3-dihydroxy-5-nitrotoluene (VIII) (2·6 g.) and stannous chloride (14·4 g.) in concentrated hydrochloric acid (24 ml.) were warmed on a steam-bath for 1 hr. After dilution with water (100 ml.) and removal of tin as sulphide, the solution was concentrated. The resulting crystals were twice recrystallised from concentrated hydrochloric acid, giving *5-amino-2 : 3-dihydroxytoluene hydrochloride* as needles, m. p. 212° (decomp.). The dry solid rapidly darkened and could not be analysed satisfactorily.

2 : 3-*Diacetoxy- and* 2 : 3-*Dibenzoyloxy-toluene.*—Acetylation of 2 : 3-dihydroxytoluene gave 2 : 3-*diacetoxytoluene*, m. p. 70—71° after recrystallisation from aqueous ethanol (Found: C, 63·4; H, 5·5. $C_{11}H_{12}O_4$ requires C, 63·4; H, 5·8%). Benzoylation of the same catechol gave 2 : 3-*dibenzoyloxytoluene* as plates, m. p. 121—122° after three crystallisations from methanol (Found: C, 75·8; H, 4·8. $C_{21}H_{16}O_4$ requires C, 75·9; H, 4·8%).

Reaction of 2 : 6-*Dichloro-*p-*benzoquinone* 4-*Chloroimide with Resorcinol Monomethyl Ether.*—The dichloro-chloroimide (1·0 g.) (Apte and Panse, *J. Indian Chem. Soc.*, 1947, **24**, 375) was added gradually with vigorous stirring to resorcinol monomethyl ether (0·9 g.) and sodium hydroxide (1·1 g.) in water (21 ml.) at 0°. Stirring was continued for a further 20 min., then the precipitate was collected. It was recrystallised by dissolving it in a small volume of hot water and adding a hot saturated brine solution until the sodium salt of the indophenol began to separate. After two repetitions of this process, the indophenol was dissolved in water and acidified with dilute hydrochloric acid. The precipitate of free *indophenol* was collected, well washed with water, and dried in a vacuum-desiccator. Two samples from different preparations were analysed (Found: C, 51·4, 51·5; H, 3·4, 3·3; N, 4·3, 4·2; Cl, 21·3, 21·4; OMe, 10·0, 10·3. $C_{12}H_8O_3NCl_3$·OMe requires C, 52·4; H, 3·0; N, 4·7; Cl, 23·8; OMe, 10·4. $C_{13}H_8O_3NCl_3$·OMe requires C, 51·2; H, 3·4; N, 4·3; Cl, 21·6; OMe, 9·5%). The sodium salt is stable and gives a deep blue solution in water, which becomes brown when acidified. Reductive acetylation of the compound by zinc dust, acetic anhydride, and acetic acid gave an uncrystallisable yellow oil.

One of us (I. M. W.) thanks the University of Bristol for a Graduate Scholarship.

THE UNIVERSITY, BRISTOL.

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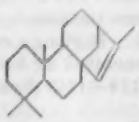
Infrared Spectra of Natural Products. Part IV. The Structure of Phyllocladene.*

By W. Bottomley, A. R. H. Cole, and D. E. White.

[Reprint Order No. 6217.]

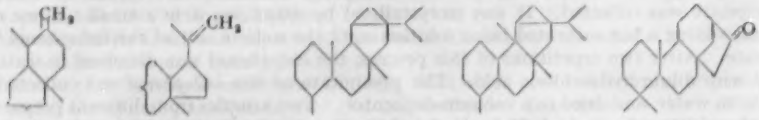
Infrared measurements on phyllocladene (I), a nor-ketone (VII) obtained from it, and *iso*phyllocladene (II) lend support to structures put forward by Brandt. For (I) the presence of a vinylidene group attached to a five-membered ring, with one adjacent methylene group, is shown. The methyl-group absorption indicates the presence of one *gem*-dimethyl group and one angular methyl group between two six-membered rings. The trisubstituted double bond and extra methyl group in (II) are confirmed.

The crystalline diterpene phyllocladene ($C_{20}H_{32}$) was first isolated by Baker and Smith ("The Pines of Australia," p. 419, Technological Museum, Sydney, N.S.W., 1910). Later work on phyllocladene and the related *iso*phyllocladene has been summarised by Simonsen and Barton ("The Terpenes," Vol. III, Cambridge University Press, 1952) and by Brandt (*New Zealand J. Sci. Tech.*, 1952, **34**B, 46) who suggested that phyllocladene is represented by (I) and *iso*phyllocladene by (II). Although no evidence was given, the *gem*-dimethyl group was placed at $C_{(1)}$ and the angular methyl group at $C_{(12)}$, by analogy with similar diterpenoids of known structure.

(I)  (II)

We have now measured the infrared spectra of phyllocladene, *iso*phyllocladene, and the nor-ketone obtained by oxidation of the former with osmium tetroxide–periodic acid. The results are consistent with the formulæ (I) and (II), although the infrared data do not give all the desired information about the carbon skeleton.

Phyllocladene shows the three characteristic bands of the vinylidene group at 3069 ($=C\langle^{H}_{H}$ stretching), 1657 ($\varepsilon_{max.} = 56$, C=C stretching), and 872 cm.$^{-1}$ ($=C\langle^{H}_{H}$ bending). The relatively high frequency of the C=C stretching vibration indicates that the vinylidene group is attached to a slightly strained ring. It might be compared, for example, with values of 1647 cm.$^{-1}$ (Nujol mull) for (III) (Ames, Beton, Bowers, Halsall, and Jones, *J.*, 1954, 1905) and 1640 cm.$^{-1}$ (in carbon tetrachloride) for lupeol (IV). Bladon, Fabian, Henbest, Koch, and Wood (*J.*, 1951, 2402) have pointed out that ring strain has the effect of strengthening exocyclic bonds and weakening the cyclic bonds.



(III) (IV) (V) (VI) (VII)

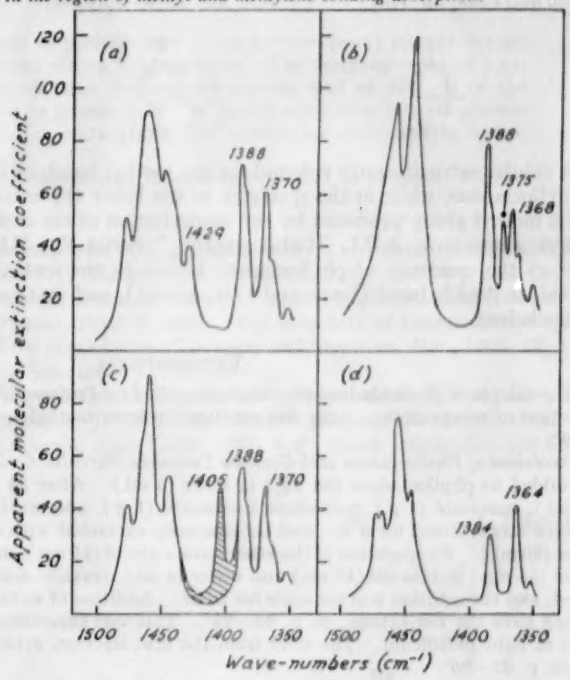
Phyllocladene has no band at 3040 cm.$^{-1}$ (Cole, *J.*, 1954, 3807), indicating that it has no methylene group in a three-membered ring as would be required by the structures (V) or (VI) suggested for α-dihydrophyllocladene by Soltys (*Monatsh.*, 1929, **53–54**, 175).

The nor-ketone (VII, if I is correct) shows a carbonyl band at 1742 cm.$^{-1}$, proving conclusively that in phyllocladene the vinylidene group is attached to a five-membered ring. Furthermore, there is a band at 1405 cm.$^{-1}$ in the region of methyl and methylene bending absorption (see Fig.). This must be due to one or two methylene groups adjacent

* Part III, *J.*, 1954, 3810.

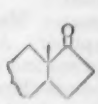
to the carbonyl group (Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648). A quantitative measurement of the area under the band (see p. 2626) shows that there is one methylene group adjacent to the carbonyl. The shaded portion corresponds to an area of 330 units [cf. 320 for 17-oxoandrostan-3β-yl acetate (VIII; 1407 cm.$^{-1}$) which has one adjacent methylene group, and 620 for A-norcholestanone (IX; 1410 cm.$^{-1}$) which has two (Barnes,

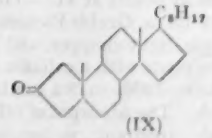
Infrared spectra in the region of methyl and methylene bending absorption.



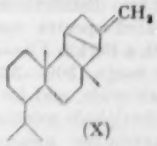
(*a*) *Phyllocladene*
(*b*) iso*Phyllocladene*
(*c*) *Nor-ketone* (VII)
(*d*) 1 : 1-*Dimethylcyclohexane*

Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571)]. The carbonyl frequency eliminates the possibility of the four-membered ring structure (X) suggested by Uota (*J. Dept. Agric. Kyushu Imp. Univ.*, 1937, **5**, 118, quoted by Brandt, *loc. cit.*) for phyllocladene.


(VIII)



(IX)

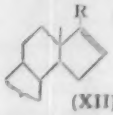


(X)

*iso*Phyllocladene has bands at 3037 (=C–H stretching), 1635 ($\epsilon_{max.}$ = 18, C=C stretching), and 825 cm.$^{-1}$, all of which are characteristic of a trisubstituted double bond. The marked decrease in intensity of the C=C stretching absorption due to the increase in symmetry of the double bond on isomerisation from phyllocladene should be noted. The fairly high intensity of the band at 3037 cm.$^{-1}$ and the relatively low frequency of the C=C stretching band are due to the presence of considerable strain in the five-membered bridged ring [cf. 1645 cm.$^{-1}$ for 1 : 4 : 4-trimethyl*cyclo*pentene (XI; A.P.I. "Catalogue of Infrared Spectra," Serial No. 213) which has very little strain, and 1621—1630 cm.$^{-1}$ for Δ^{16}-steroids (XII; Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252) in which the five-membered ring is quite strained. The region of methyl absorption (1350—1400 cm.$^{-1}$) due to bending vibrations (Jones and Cole, *loc. cit.*) is shown in the Figure.

In the spectrum of 1 : 1-dimethyl*cyclo*hexane (XIII) the *gem*-dimethyl group gives bands at 1384 and 1364 cm.$^{-1}$ with an intensity ratio of 0·75 : 1. It will be noticed that in the methyl region of phyllocladene the bands at 1388 and 1370 cm.$^{-1}$ have a ratio of intensity of approximately 1·2 : 1, and there is a suggestion of a shoulder at 1385 cm.$^{-1}$. This means that there are two bands contributing to the upper peak, and near 1385—1388 cm.$^{-1}$ is just the expected frequency for an angular methyl group between two six-membered rings (Jones and Cole, *loc. cit.*).

(XI)



(XII)

(XIII)

A similar intensity ratio is found for the methyl bands of the nor-ketone (VII) and for *iso*phyllocladene, while in the spectrum of the latter the extra band at 1375 cm.$^{-1}$ is due to the methyl group produced by the isomerisation of the double bond (cf. 1375 cm.$^{-1}$ for methyl*cyclo*pentane, A.P.I. "Catalogue,etc.," Serial No. 511). The small band at 1429 cm.$^{-1}$ in the spectrum of phyllocladene is due to the methylene group adjacent to the vinylidene double bond (Jones and Cole, *loc. cit.*), and disappears on isomerisation to *iso*-phyllocladene.

Experimental

The sample of phyllocladene was kindly supplied by Professor A. J. Birch from H. G. Smith's collection of compounds. After recrystallisation from methylene chloride–methanol it melted at 96°.

Oxidation of Phyllocladene with Osmium Tetroxide–Periodic Acid.—Osmium tetroxide (0·16 g.) was added to phyllocladene (58 mg.) in ether (5 ml.). After 24 hr. benzene (10 ml.), ethanol (10 ml.), mannitol (1 g.), potassium hydroxide (1 g.), and water (10 ml.) were added. The mixture was refluxed for 6 hr., and continuously extracted with ether (5 hr.) after addition of water (30 ml.). Evaporation of the ether gave a glycol (35 mg.), m. p. 165—167°. To the crude glycol (35 mg.) in ethanol (18 ml.) and water (4 ml.), periodic acid (0·2 g.) in water (2 ml.) was added, and the solution was set aside for 26 hr. Addition of water, evaporation of ethanol, and cooling gave the nor-ketone, m. p. 86—95°. This was chromatographed on alumina (activity I–II) in light petroleum. The solid from the first fraction, after sublimation at 50°/0·2 mm., had m. p. 93—95°.

*iso*Phyllocladene.—This was prepared from phyllocladene by using alcoholic sulphuric acid as described by Brandt (*loc. cit.*). After recrystallisation from ethanol it melted at 107·5—109°.

1 : 1-*Dimethylcyclohexane*.—This was prepared from dimedone semicarbazone as described by Seibert (*Chem. Ber.*, 1947, **80**, 494), except that a glass flask instead of a copper vessel was used. After two distillations over sodium, it boiled at 117—118°, n_D^{20} 1·4250.

The infrared spectra were measured on a Grubb-Parsons Spectrometer, Model S.3.A., equipped with a Perkin-Elmer thermocouple, light chopper, and No. 81 amplifier. All measurements in the range 1300—3200 cm.$^{-1}$ were made with a calcium fluoride prism and solutions in carbon tetrachloride, and for the range 650—1300 cm.$^{-1}$ a double-pass sodium chloride system and carbon disulphide solutions were used. The absorption cell was 1·3 mm. in thickness.

For quantitative measurements the apparent molecular extinction coefficient $\varepsilon = [\log_{10}(T_o/T)]/cl$ (Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72) was employed. With the resolving power available in our spectrometer, these values do not differ from the true molecular extinction coefficients by more than 2—3%. When determining the area of the band due to the methylene group adjacent to the carbonyl of (VII) a true graphical separation of overlapping bands was not carried out, but approximately the same proportion of the area was integrated as in the earlier publication (Barnes *et al.*, *loc. cit.*).

The infrared spectrometer was obtained through a generous grant from the Nuffield Foundation, to whom one of us (A. R. H. C.) is also indebted for a Fellowship.

University of Western Australia,
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[*Received, March 9th*, 1955.]

The Mechanism of the Rearrangement of Pinonic Acid into Homoterpenyl Methyl Ketone.

By C. L. Arcus and G. J. Bennett.

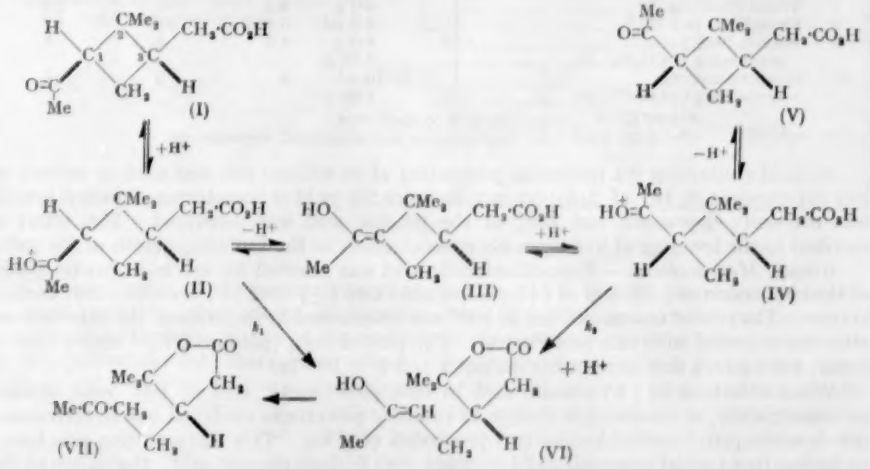
[Reprint Order No. 6247.]

The rearrangement of pinonic acid (I) to homoterpenyl methyl ketone (VII) requires relatively strong acid-catalysis. The rearrangement of (±)- and of (+)-*trans*-pinonic acid, in monochloroacetic acid at 100°, is of the first-order with regard to pinonic acid. A partial conversion into *cis*-pinonic acid occurs in the acidic solution, but this isomer also rearranges to homoterpenyl methyl ketone.

An intramolecular mechanism, represented in (IX), is proposed for the rearrangement.

Pinonic acid (I), on being heated with 50% sulphuric acid, is converted in high yield into homoterpenyl methyl ketone (VII) (Baeyer, *Ber.*, 1896, **29**, 326); the (+)- and the (−)-form of this compound have been obtained from (+)- and (−)-pinonic acid (Barbier and Grignard, *Bull. Soc. chim. France*, 1910, **7**, 548). The structure of homoterpenyl methyl ketone has been ascertained by degradation (Tiemann and Semmler, *Ber.*, 1895, **28**, 1778) and by synthesis (J. Owen and Simonsen, *J.*, 1932, 1424).

The data relating to the degradation and synthesis of pinonic acids (Baeyer, *Ber.*, 1896, **29**, 3, 1909; Perkin and Simonsen, *J.*, 1909, **95**, 1176; Gallas and Montañeš, *Anal. Fis. Quim.*, 1930, **28**, 1196; Grandperrin, *Ann. Chim.*, 1936, **6**, 5; Guha, Ganapathi, and Subra-



manian, *Ber.*, 1937, **70**, 1505; Rao, *J. Indian Chem. Soc.*, 1943, **20**, 97) yield no decisive evidence on geometrical configurations, mainly owing to the use (largely unavoidable) of reagents which catalyse enolisation, leading to geometrical isomerisation. The assignment of geometrical configurations to (+)- and (±)-pinonic acids made by Simonsen and L. N. Owen ("The Terpenes," University Press, Cambridge, 1949, Vol. II, p. 147)—that the solid acids are *trans* and the liquid acids *cis*—has been adopted. The opposite configurations have been used by Delépine and Badoche (*Compt. rend.*, 1952, **235**, 1455), but no essential alteration to the mechanisms which have been deduced (below) becomes necessary if these authors' configurations are adopted.

The essential step in the conversion of (I) into (VII) is the rearrangement of an aceto-*cyclo*butylacetic acid to a keto-γ-lactone. Reaction schemes postulating the intermediate tertiary alcohol (VIII) have been proposed (Simonsen and Owen, *op. cit.*, p. 117; Delépine and Badoche, *loc. cit.*), but no experimental evidence for its occurrence has been adduced.

$$\begin{matrix} & CMe_2{\cdot}OH & \\ COMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH{\cdot}CH_2{\cdot}CO_2H & & \\ & \text{(VIII)} & \end{matrix}$$

In experiments preliminary to rate-measurements, the percentage conversion of pinonic acid into homoterpenyl methyl ketone, in acid solvents at 100° for stated times, has been determined; the results are collected in Table 1. In a number of instances the keto-lactone was converted into its 2 : 4-dinitrophenylhydrazone, of which the yield (based on the pinonic acid) is given in the last column.

It is apparent from Table 1 that the strongly acidic media, phosphoric, trichloroacetic, and 99% formic acids, cause rapid rearrangement, that acetic acid is ineffective, and that monochloroacetic and 90% formic acids occupy an intermediate position.

The rearrangement proceeds smoothly, and no by-products have been encountered; prolonged heating in phosphoric acid effects a breakdown of homoterpenyl methyl ketone which is to be described later.

TABLE 1. *The conversion of (±)-pinonic acid into (±)-homoterpenyl methyl ketone.*

Expt. no.*	Acid	Quantity	Time (hr.)	Yield (%) of homoterpenyl methyl ketone: direct	Yield (%) of homoterpenyl methyl ketone: from 2 : 4-dinitrophenylhydrazone
1	Acetic	4·0 g.	4·5	Nil	—
2	Formic (90%)	4·0 g.	4·5	55	51
3	Formic (99%)	to 10 ml.	2	73	—
4[a]	Monochloroacetic	4·0 g.	3·5	17	15
5	,,	to 10 ml.	9	58	—
6	,,	to 10 ml.	30	95	—
7	Trichloroacetic	4·0 g.	4·5	100	94
8	Phosphoric (*d* 1·72)	4·0 ml.	5 min.	95	92
9[b]	Formic (90%) containing $H{\cdot}CO_2Na$	4·0 g. 0·53 g.	4·5	1	1
10[c]	Monochloroacetic containing $CH_2Cl{\cdot}CO_2Na$	to 10 ml. 1·80 g.	9	5	4

* 1·00 G. of (±)-pinonic acid in each expt.

[a,b,c] 0·74, 0·85, 0·85 G. of pinonic acid recovered, respectively.

An acid containing 0·1 molecular proportion of its sodium salt was used as solvent in two experiments (9, 10; cf. 2, 5); in each instance the yield of homoterpenyl methyl ketone was markedly depressed, and 85% of the pinonic acid was recovered. This effect is ascribed to the lowering of hydrogen-ion concentration by the buffering action of the salts.

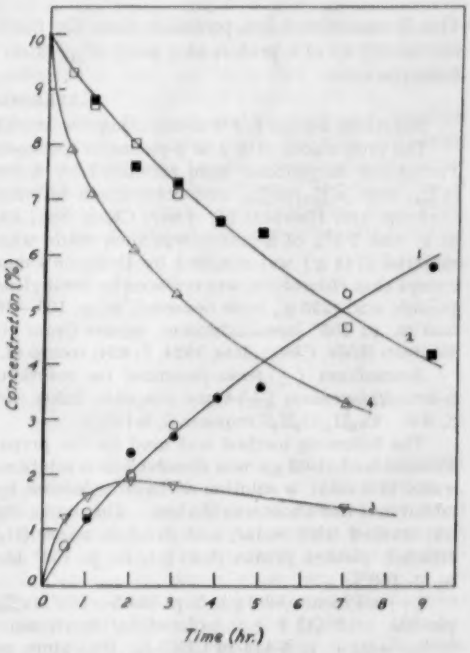
Kinetic Measurements.—Monochloroacetic acid was selected for use in a kinetic study of the conversion of (±)- and of (+)-pinonic acid into (±)- and (+)-homoterpenyl methyl ketone. The rate of rearrangement at 100° was determined by isolation of the keto-lactone after the recorded intervals (see Figure). The plot of $\log_{10}$ [pinonic acid]$^{-1}$ *versus* time is linear, and yields a first-order rate constant $k = 9{\cdot}9 \times 10^{-2}$ hr.$^{-1}$.

When solutions of (+)-pinonic acid in monochloroacetic acid at 100° were studied polarimetrically, a considerable change in rotatory power was observed before conversion into homoterpenyl methyl ketone had proceeded very far. This mutarotation was found to be due to a partial conversion of (+)-*trans*- into (−)-*cis*-pinonic acid; the oxime of the latter was prepared from the pinonic acid recovered from "mutarotated" solutions. In addition, the oxime of (±)-*cis*-pinonic acid was prepared from pinonic acid recovered from the rate-experiments with (±)-*trans*-pinonic acid.

The specific rotations (*c*, 5 in $CHCl_3$) of the specimens of optically active pinonic acid recovered from the kinetic experiments were determined. The corresponding value is known for (+)-*trans*-pinonic acid: $[\alpha]_{5893}$ +92·4° (present observation; Delépine and Badoche, *Ann. Chim.*, 1950, **5**, 153, record $[\alpha]_{5893}$ +95°), and for (−)-*cis*-pinonic acid: $[\alpha]_{5893}$ −81·5° (*idem, loc. cit.*), whence were calculated the proportions of these isomers in the above specimens of pinonic acid. The concentrations of total, *trans*-, and *cis*-pinonic acid are plotted *versus* time in the Figure.

The Mechanism of Rearrangement, and of trans–cis-*Isomerisation.*—The mechanism of the conversion of *trans-* into *cis*-pinonic acid is probably identical with that for the acid-catalysed racemisation of ketones CHRR'·CO·R" (Bartlett and Stauffer, *J. Amer. Chem. Soc.*, 1933, **55**, 4992; 1935, **57**, 2580; Ingold and Wilson, *J.*, 1934, 773). When this mechanism is applied to *trans-* and *cis*-pinonic acid (I—V), the inversion of configuration at $C_{(1)}$ results in the appropriate geometrical isomerisation.

During the first 1·9 hours *cis*-pinonic acid accumulates in the system more rapidly than does homoterpenyl methyl ketone, and, from tangents drawn at the origin to curves 3 and 1, the rate constant for *trans*-acid ⟶ *cis*-acid is approximately twice that for *trans*-acid ⟶ keto-lactone.

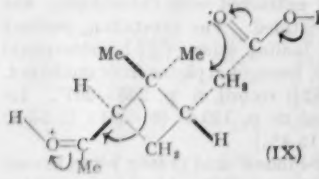


Rearrangement and isomerisation of trans-*pinonic acid in monochloroacetic acid at* 100°.

(1) Homoterpenyl methyl ketone, ○
(2) Total pinonic acid, □
(3) *cis*-Pinonic acid, ▽
(4) *trans*-Pinonic acid, △

" Open " points were determined with (+)-*trans*-pinonic acid, and " solid " points with (±)-*trans*-pinonic acid.

The mechanism of the rearrangement of pinonic acid to homoterpenyl methyl ketone is, most probably, that shown in formulæ (I—VII). (The geometrical configurations given to the ethylenic groups of the enols have no significance.) The act of conversion of the *cyclo*butane into the lactone ring is the rearrangement of the protonated *trans-* or *cis*-pinonic acid (II or IV). Models of these molecules show the carboxyl group to be well placed to enter into a replacement reaction at $C_{(2)}$. The steric relations, together with the tautomeric electron movements whereby rearrangement occurs, are represented in (IX).


(IX)

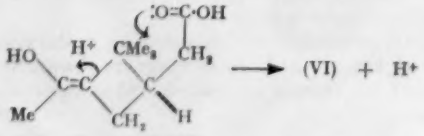
It has been found, above, that the rate of formation of homoterpenyl methyl ketone is proportional to the total concentration of (*trans-* + *cis-*)pinonic acid, and it is inferred from this result that the rate constants k_1 and k_2, relating to (II) and (IV) respectively, do not differ appreciably.

Three apparently possible mechanisms, briefly described below, have been considered and rejected.

The rate of formation of homoterpenyl methyl ketone is, as has been stated, proportional to the concentration of (*trans-* + *cis-*)pinonic acid : were the *trans*-acid (or its proton

adduct) the sole precursor, then the curve for the formation of the keto-lactone (curve 1) would show an initial rapid fall in slope, and were the *cis*-acid (or its proton-adduct) the sole precursor, this curve would have a sigmoid form.

A tenable mechanism is that postulating the enol (III) as the sole presursor to the keto-lactone:



This is considered less probable than the mechanism adopted above, because it involves the taking up of a proton at a point ($C_{(1)}$) from which a proton has earlier been released to form the enol.

Experimental

Rotations are for *l*, 2·0 unless otherwise stated.

The proportions of α- and β-pinene in specimens of (−)- and (+)-pinene from American and Portuguese turpentines were estimated by determination of the rotatory dispersions $[\alpha]^{25}_{5461}/[\alpha]^{25}_{5893}$ and $[\alpha]^{25}_{5461}/[\alpha]^{25}_{6708}$, and comparison of these values with the Tables given by Fuguitt, Stallcup, and Hawkins (*J. Amer. Chem. Soc.*, 1942, **64**, 2978). A mixture containing 97·5% of α- and 2·5% of β-pinene was then made which had b. p. 156—158°, $[\alpha]^{20}_{5893}$ −0·54°; this material (748 g.) was oxidised by Delépine's method (*Bull. Soc. chim. France*, 1936, **3**, 1369) except that chloroform was replaced by methylene chloride as extractant; it yielded (±)-*trans*-pinonic acid (336 g., from benzene), m. p. 103—104°, which on recrystallisation from hot water had m. p. 105° [semicarbazone, prisms (from ethanol), m. p. 217° (decomp.); Ruzicka and Pontalti (*Helv. Chim. Acta*, 1924, **7**, 494) record m. p. 208°].

Ammonium (±)-*trans*-pinonate, on reaction with *S*-benzylthiuronium chloride, yielded *S-benzylthiuronium* (±)-trans-*pinonate*, flakes (from ethanol), m. p. 152° (decomp.) (Found: S, 9·0. $C_{18}H_{26}O_2N_2S$ requires S, 9·15%).

The following method was used for the preparation of all pinonic acid oximes: (±)-*trans*-Pinonic acid (1·00 g.) was dissolved in a solution of potassium hydrogen carbonate (0·55 g.) in water (2·0 ml.); a solution of hydroxylamine hydrochloride (0·42 g.) in water (1·0 ml.) was added and the whole was shaken. The oxime separated and solidified; it was crushed, filtered off, washed with water, and dried *in vacuo* (H_2SO_4). It (0·85 g.), on recrystallisation from ethanol, yielded prisms (0·55 g.), m. p. 152° (decomp.) (Baeyer, *Ber.*, 1896, **29**, 24, records m. p. 150°).

(+)-α-Pinene (68·0 g.), b. p. 154·5—156°, $[\alpha]^{20}_{5893}$ +47·0°, on similar oxidation gave (+)-*trans*-pinonic acid (17·3 g.; isolated by fractional crystallisation from ether), m. p. 68—69°, $[\alpha]^{24}_{5893}$ +92·4° (*c* 5·443 in $CHCl_3$). Its oxime, needles from ethanol–water (1 : 4), had m. p. 135·5°, $[\alpha]^{20}_{5893}$ +51·7° (*c*, 5·102 in $CHCl_3$) (Found: C, 60·2; H, 8·7; N, 7·3. Calc. for $C_{10}H_{17}O_2N$: C, 60·3; H, 8·6; N, 7·05%). Delépine (*loc. cit.*) records m. p. 128°.

(±)-*Homoterpenyl Methyl Ketone*.—The following preparation is based on the brief description given by Baeyer (*loc. cit.*). (±)-*trans*-Pinonic acid (6·0 g.) was heated with aqueous sulphuric acid (50%; 60 g.) at 100° for 30 min., and the solution was poured into water (150 ml.). The product was salted out with ammonium sulphate and extracted with chloroform; the extract was washed and dried (Na_2SO_4), and the solvent distilled. The crystalline product (5·4 g.) yielded, on recrystallisation from the minimum of boiling ether, (±)-homoterpenyl methyl ketone (3·4 g.), prisms, m. p. 60·5°. Its semicarbazone, hexagonal plates from methanol, had m. p. 206—207°; J. Owen and Simonsen (*J.*, 1932, 1424) record m. p. 206—207°. Its 2 : 4-*dinitrophenylhydrazone*, orange needles from ethanol, had m. p. 163·5° (Found: C, 53·1; H, 5·6; N, 14·9. $C_{16}H_{20}O_5N_4$ requires C, 52·7; H, 5·55; N, 15·4%).

Rearrangement in the acidic solvents of Table 1. (±)-*trans*-Pinonic acid (1·00 g.) was heated at 100° in the solvent, and for the time, stated in the Table; water (100 ml.) was then added and the whole was made slightly alkaline (to methyl red) with ammonia and extracted with methylene chloride (25, 20, 15, 10, 10 ml. portions successively); the extract was washed with water (2 × 25 ml.) and distilled (water forms an azeotrope with methylene chloride). The homoterpenyl methyl ketone was dried at 100° (30 min.) or *in vacuo* at ordinary temperature.

Unconverted pinonic acid was recovered from the extracted aqueous solution by acidification with hydrochloric acid and extraction as above.

(These procedures for the isolation of the keto-lactone and pinonic acid were used in the rate-measurements, below.)

The preparation of the 2 : 4-dinitrophenylhydrazone of (±)-homoterpenyl methyl ketone was standardised as follows: to a solution of the keto-lactone (1·00 g.; reagents proportional to the actual weight were taken) in warm propan-2-ol (15 ml.), 2 : 4-dinitrophenylhydrazine (1·1 g.) was added; the solution was boiled, and addition of a few drops of concentrated hydrochloric acid then precipitated the derivative; further propan-2-ol (15 ml.) was added, and the suspension was cooled and filtered. The 2 : 4-dinitrophenylhydrazone was washed with propan-2-ol (30 ml.), dried at 120°, and weighed. Its m. p. and mixed m. p. were determined. In a control experiment (±)-homoterpenyl methyl ketone (0·50 g.) gave 0·95 g. (95%) of the derivative.

Rate of rearrangement. Monochloroacetic acid was fused, and 0·05 mol. of concentrated aqueous sodium hydroxide was cautiously added; distillation then gave a main fraction having b. p. 101—102°/25 mm. The liquid was allowed to solidify to the extent of about 90% and the remaining liquid was drained off and discarded; the solid was re-melted and the process repeated; the acid so purified had equiv. 94·31 (Calc. for $CH_2Cl{\cdot}CO_2H$: equiv., 94·50).

(±)-*trans*-Pinonic acid (1·00 g.) was weighed into a 10-ml. graduated flask and dissolved in monochloroacetic acid at 80°; the solution was made up to the mark, the flask was sealed with a Polythene cap, and thereafter immersed in a steam-bath for the time(s) recorded in the Figure; homoterpenyl methyl ketone was then isolated as described above. The quantities of keto-lactone formed by rearrangement of (±)- and (+)-pinonic acid, together with those calculated from the first experimental point ($t = \frac{1}{2}$ hr.) by use of the first-order rate-constant $k = 9{\cdot}9 \times 10^{-2}$ hr.$^{-1}$, are as follows:

t (hr.)		½	1	1	2	2	3
Pinonic acid		+	+	±	+	±	+
Homoterpenyl methyl ketone	isolated (g.)	0·07	0·13	0·12	0·20	0·24	0·29
	calc. (g.)	same	0·11	0·11	0·20	0·20	0·27
t (hr.)		3	4	5	7	9	
Pinonic acid		±	±	±	+	±	
Homoterpenyl methyl ketone	isolated (g.)	0·27	0·34	0·36	0·53	0·58	
	calc. (g.)	0·27	0·34	0·40	0·51	0·60	

Specimens of pinonic acid recovered from the rate-experiments were combined and washed with ethanol, whereby they were separated into (±)-*trans*-pinonic acid, m. p. and mixed m. p. 102°, and a liquid mixture of this acid and the (±)-*cis*-isomer. This mixture was converted into the mixed oximes, from which, by fractional crystallisation from ethanol, there were isolated (±)-*cis*-pinonic acid oxime, m. p. 171° [Delépine (*loc. cit.*) records m. p. 168°], and also the more soluble *trans*-oxime, as prisms, m. p. 151° alone and when mixed with the specimen above.

(+)-*Homoterpenyl Methyl Ketone.—Mutarotation of solutions of pinonic acid in monochloroacetic acid.* A solution of (+)-*trans*-pinonic acid [(i), (ii) 1·000 g.; (iii), (iv) 1·750 g.] in monochloroacetic acid (to 10 ml. at 80°) was placed in a 1-dm. jacketed polarimeter tube with sealed end-plates, maintained at 100° by steam passing freely through the jacket. The rotatory power of the solution was determined at intervals (Table 2); the first reading was made within 5 min. of the preparation of the solution.

The liquid mixture of (+)-*trans*- and (−)-*cis*-pinonic acids (6·3 g.) recovered from these

TABLE 2.

	Time (min.):	0	5	10	20	30	40	60	80	100
(i)	α^{100}_{5893}	5·46°	5·18°	4·92°	4·50°	4·10°	3·87°	3·46°	3·18°	3·02°
(ii)	α^{100}_{5893}	5·53	5·24	4·99	4·54	4·18	3·90	3·44	3·21	3·04
(iii)	α^{100}_{5893}	9·34	8·85	8·39	7·69	6·88	6·65	5·92	5·41	5·10
(iv)	α^{100}_{5893}	9·55	9·07	8·67	7·90	7·33	6·82	6·05	5·52	5·18
	Time (min.):	120	140	150	180	195	210	230	240	
(i)	α^{100}_{5893}	2·94°	2·89°	2·89°	—	2·89°	2·91°			
(ii)	α^{100}_{5893}	2·92	2·87	2·87	—	2·87	2·88			
(iii)	α^{100}_{5893}	4·87	4·77	4·73	4·67°	—	—	4·67°	4·67°	
(iv)	α^{100}_{5893}	4·93	4·78	4·71	4·65	—	4·63	4·69	4·69	

polarimetric experiments was heated with thrice its volume of phosphoric acid (*d* 1·72) for 10 min. at 100°. The product (5·95 g.), isolated as described for the (±)-keto-lactone, was

recrystallised from ether and yielded (+)-homoterpenyl methyl ketone (3·5 g.), m. p. 46·5°, $[\alpha]_{5893}^{20}$ +58·6° (*c* 5·271 in $CHCl_3$), $[\alpha]_{5893}^{100}$ +45·5° (*c*, 5·612 in $CH_2Cl{\cdot}CO_2H$) and $[\alpha]_{5893}^{100}$ +45·8° (*c*, 10·000 in $CH_2Cl{\cdot}CO_2H$; the rotation was unchanged after 4 hr. at 100°); it gave a 2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol), m. p. 168·5° (Found : C, 53·0; H, 5·7; N, 15·5%). Both Barbier and Grignard (*loc. cit.*) and Delépine and Badoche (*Compt. rend.*, 1952, **235**, 1069) record m. p. 47° for (+)-homoterpenyl methyl ketone.

Rate of rearrangement. Five determinations (cf. Figure) of the conversion of (+)-*trans*-pinonic acid into (+)-homoterpenyl methyl ketone, with recovery of unconverted pinonic acid, were carried out by the method described for the (±)-keto-lactone. The specific rotation (*c*, 5 in $CHCl_3$) of the recovered pinonic acid was determined :

Reaction-time (hr.)	0·5	1	2	3	7
$[\alpha]_{5893}^{t}$	+66·7°	+57·4°	+47·0°	+43·4°	+39·7°
t	22°	22°	21°	20°	22°

The specimens of (+)-keto-lactone isolated during these rate-experiments were combined (1·60 g.), dissolved in hot water (20 ml.), treated with charcoal to remove methyl red, extracted with methylene chloride, and twice recrystallised from ether–light petroleum (b. p. 40—60°); the (+)-homoterpenyl methyl ketone formed prisms (0·57 g.), m. p. 46—47°, $[\alpha]_{5893}^{17}$ +59·6° (*c*, 5·013 in $CHCl_3$).

The specimens of semisolid pinonic acid recovered from the above rate-experiments were pressed on filter paper; the solid was removed and the paper extracted with methylene chloride. The extract yielded a liquid acid (2·16 g.) which was converted into its oxime (1·72 g.); after extraction with boiling ether there remained a product (0·69 g.), m. p. 195°, which by repeated recrystallisation from hot ethanol yielded (−)-*cis*-pinonic acid oxime, prisms, m. p. 199·5—200°, $[\alpha]_{5893}^{20}$ −34·3° (*l*, 4; *c*, 0·437 in ether) (Found : C, 60·5; H, 8·7; N, 7·2%). For this oxime Delépine (*loc. cit.*) records m. p. 192° and $[\alpha]_{5893}$ −29·5° (in ether).

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Nucleotides Part XXXII. Synthesis of a Dithymidine Dinucleotide Containing a 3′ : 5′-Internucleotidic Linkage.*

By A. M. Michelson and Sir Alexander R. Todd.

[Reprint Order No. 6258.]

A dithymidine dinucleotide (V) has been synthesised by condensing 3′-*O*-acetylthymidine with thymidine 3′-(benzyl phosphorochloridate) 5′-(dibenzyl phosphate) and subsequently removing the protecting groups. This represents the first preparation of a dinucleotide by chemical means and since the synthetic material behaves towards enzymes exactly as the dinucleotidic fragments obtained by degrading deoxyribonucleic acids the postulate of a 3′ : 5′-internucleotidic linkage in the latter is further confirmed. Thymidine-3′ thymidine-5′ phosphate has also been prepared and by-products isolated include a dinucleoside pyrophosphate and a dinucleotide pyrophosphate.

In previous papers of this series we have described the preparation of the 3′- and 5′-phosphates of the natural deoxyribonucleosides thymidine (I; R = R′ = H) (Michelson and Todd, *J.*, 1953, 951), deoxycytidine (Michelson and Todd, *J.*, 1954, 34), deoxyadenosine and deoxyguanosine (Hayes, Michelson, and Todd, *J.*, 1955, 808), and have identified the

* Part XXXI, *J.*, 1955, 2206.

5′-phosphates with the deoxyribonucleotides obtained by enzymic degradation of deoxyribonucleic acids, thus confirming the structures proposed by Carter (*J. Amer. Chem. Soc.*, 1951, **73**, 1573). The formulation of the deoxyribonucleic acids as 3′ : 5′-linked linear polynucleotides (cf. *inter al.*, Brown and Todd, *J.*, 1952, 52) is supported, *e.g.*, by this identification and by the isolation of the 3′ : 5′-diphosphates of thymidine and deoxycytidine from acid hydrolysates (Dekker, Michelson, and Todd, *J.*, 1953, 947). As a result of these studies it became possible to proceed to the next phase of our synthetic programme and to attempt the preparation of 3′ : 5′-linked dideoxyribonucleotides by unambiguous routes so that they could be compared in their behaviour with dinucleotides occurring in deoxyribonuclease digests of deoxyribonucleic acids. A number of such dinucleotides have been separated from deoxyribonuclease digests in solution, although not isolated in substance, and their behaviour towards various enzymes has been described (Markham and Smith, *Biochim. Biophys. Acta*, 1952, **8**, 350; Sinsheimer, *J. Biol. Chem.*, 1954, **208**, 444). Hitherto no synthesis of a dinucleotide by chemical as distinct from enzymic methods has ever been accomplished either in the ribo- or the deoxyribo-nucleotide series.

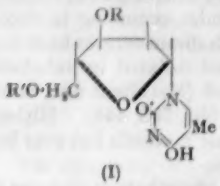
In exploratory work we endeavoured to prepare a dinucleoside phosphate containing the 3′ : 5′-internucleotidic linkage by treating the silver salt of deoxycytidine-3′ benzyl phosphate with 3′-*O*-acetyl-5′-deoxy-5′-iodothymidine under a variety of conditions; all attempts failed, however, and other methods had to be sought. Hayes, Michelson, and Todd (*loc. cit.*) prepared the monoacetyl derivatives of deoxyadenosine and deoxyguanosine by partial deacetylation of the corresponding 3′ : 5′-diacetyl compounds. The same method, applied to 3′ : 5′-di-*O*-acetylthymidine (I; R = R′ = Ac) yielded a mixture of 5′- and 3′-*O*-acetylthymidine which were separated by countercurrent distribution. When treated with *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride in presence of 2 : 6-lutidine, 5′-*O*-acetylthymidine yielded 5′-*O*-acetylthymidine-3′ benzyl phosphite [I; R = PHO(O·CH_2Ph), R′ = Ac] as an unstable resin which could be converted into 5′-*O*-acetyl thymidine-3′ benzyl phosphorochloridate [I; R = PClO(O·CH_2Ph), R′ = Ac] by reaction with *N*-chlorosuccinimide. No attempt was made to purify the phosphorochloridate; instead it was prepared in solution from the phosphite, and it was used immediately to minimise decomposition. In small-scale preliminary experiments the phosphorochloridate appeared to react satisfactorily with 3′-*O*-acetylthymidine, giving a product containing material with the paper-chromatographic behaviour expected of a dinucleoside phosphate. Reaction of the phosphorochloridate with salts of *OO*-diphenylphosphoric acid or of trifluoroacetic acid to give mixed anhydrides, followed by treatment of these with 3′-*O*-acetylthymidine proved ineffective although a method of this type had been successfully employed in this laboratory by Dr. R. H. Hall for preparing di(ribonucleoside-5′) phosphates.

3′-*O*-Acetylthymidine was therefore allowed to react with crude 5′-*O*-acetylthymidine-3′ benzyl phosphorochloridate in presence of excess of 2 : 6-lutidine. Acetyl and benzyl groups were removed by hydrolysis and the product subjected to anion-exchange chromatography (Dowex 2 resin; chloride form). Elution with 0·01N-hydrochloric acid gave a mixture of thymidine-3′ phosphate and thymidine-3′ thymidine-5′ phosphate (II) * which were separated from one another by fractional precipitation of their calcium salts. Further elution with 0·1N-hydrochloric acid yielded di(thymidine-3′) P^1P^2-pyrophosphate (III) isolated as its calcium salt. The structure allotted to each of these products follows from their mode of preparation, analysis, and properties. The production of some dinucleoside pyrophosphate was not unexpected since hydrolysis of a phosphorochloridate in presence of base is a well-known method for preparing symmetrical pyrophosphates.

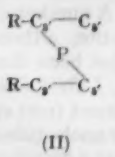
The successful synthesis of thymidine-3′ thymidine-5′ phosphate encouraged us to undertake the synthesis of a true dinucleotide by an analogous route. 3′-*O*-Acetylthymidine-5′ dibenzyl phosphate was deacetylated with methanolic ammonia and the thymidine-5′ dibenzyl phosphate so obtained was treated with *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride to give the corresponding 3′-phosphite [I; R = PHO(O·CH_2Ph), R′ = PO(O·CH_2Ph)$_2$]. This was not exhaustively purified but was treated directly with

* In formulæ (II—V) the expression R–$C_{3'}$–$C_{5'}$ has been adapted as an abbreviation for thymidine, $C_{3'}$ and $C_{5'}$ being the only sites in the deoxyribose residue bearing hydroxyl groups; P symbolises a phosphate and –P–O–P– a pyrophosphate residue.

N-chlorosuccinimide, and the crude phosphorochloridate obtained was brought into reaction with 3′-*O*-acetylthymidine in presence of 2 : 6-lutidine. One benzyl group is readily removed by acid hydrolysis from a phosphoric triester containing one or more benzyl groups; a second benzyl group is not easily removed in this way and it is usually preferable to perform this operation by catalytic hydrogenation. Since the fully protected dinucleotide formed by the reaction described would contain two phosphoric triester groupings, one (the internucleotidic linkage) bearing one, and the other (the terminal group) bearing two



(I)



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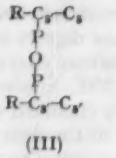

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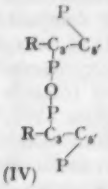
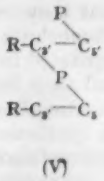


(IV)



(V)

benzyl groups, the crude reaction product was treated first with acid to remove two benzyl groups, then with barium hydroxide to effect deacetylation, and was finally hydrogenated as barium salt to complete the debenzylation. Paper chromatography showed that in addition to a trace of thymidine-5′ phosphate the product contained thymidine-3′ : 5′ diphosphate and two other substances, apparently a dinucleotide and a dinucleotide pyrophosphate. When an aqueous solution of the mixed barium salts was brought to pH 7·7 the dibarium salt of the dinucleotide pyrophosphate (IV) separated as a white precipitate. Although it contained no other nucleotide material, this salt could not be completely freed from barium phosphate and so gave unsatisfactory analytical values; the identity of its main constituent is, however, not in doubt. The mother-liquor remaining after removal of the dinucleotide pyrophosphate was subjected to anion-exchange chromatography (Dowex 2 resin; chloride form). Elution with 0·08N-hydrochloric acid gave a mixture of thymidine-3′ : 5′ diphosphate (I; R = R′ = PO_3H_2) and the dithymidine dinucleotide (V). These were separated by making use of the fact that calcium thymidine-3′ : 5′ diphosphate is much less soluble in hot water than in cold. The calcium salt of the dinucleotide (V) crystallised from water in clusters of needle-like hydrated prisms. This salt, like all the others described in this paper, could be dehydrated at 110° but was extremely hygroscopic when anhydrous; accordingly all analyses were carried out on the hydrated salts after allowing them to come to equilibrium in air.

The various thymidine derivatives described in this paper can be characterised and distinguished by paper chromatography. Distinction is also possible by paper electrophoresis in two solvents, 0·1M-potassium dihydrogen phosphate and 0·1M-disodium hydrogen phosphate; the former solvent suppresses the dissociation of secondary phosphoric groups so that migration is dependent only on the number of primary phosphoric dissociations and molecular weight, whereas in the alkaline system both primary and secondary dissociations play a part. Towards the mixture of enzymes contained in rattlesnake venom (*Crotalus atrox*) and in prostate extract the synthetic compounds behaved in the expected manner. The results are summarised in the Table. The complexities of nomenclature encountered in polynucleotides make it desirable that some abbreviated description of general applicability be devised. In the Table such an abbreviated description is used; in it T = thymidine residue, P = phosphate, and P–P = pyrophosphate, and the points of attachment of phosphate or pyrophosphate groups to thymidine are indicated by numbers. Thus the dinucleotide (V) is adequately defined by the expression T5′–P–3′T5′–P; this system of abbreviation may be applied generally in the nucleotide and polynucleotide field.

The results in the Table accord with the view that rattlesnake venom contains a 5′-nucleotidase and a phosphodiesterase, both of which are highly specific, together with a pyrophosphatase of much lower specificity (cf. Christie, Elmore, Kenner, Todd, and Weymouth, *J.*, 1953, 2947). It is worthy of note that the phosphodiesterase of rattlesnake

venom appears to be specific for esters of nucleoside-5′ phosphates; thus although it will convert both thymidine-3′ thymidine-5′ phosphate and thymidine-5′ benzyl phosphate into thymidine-5′ phosphate it is quite without action on thymidine-3′ benzyl phosphate.

Substrate	Products formed by action of: Crude rattlesnake venom	Crude prostatic phosphatase
T3′–P	No action	T
T5′–P	T	T
P–3′T5′–P	No action	T
T3′–P–5′T	T	T *
T5′–P–3′T5′–P	T	T3′–P–5′T + T
T3′–P–P–3′T	T3′–P *	T *
P–5′T3′–P–P–3′T5′–P	P–3′T5′–P *	T3′P–P–3′T + T

* Unchanged starting material also present.

Prostate extract shows phosphomonoesterase and phosphodiesterase as well as weak pyrophosphatase activity.

Purified prostate phosphomonoesterase converted the synthetic dinucleotide into thymidine-3′ thymidine-5′ phosphate, and the dinucleotide pyrophosphate into di(thymidine-3′) P^1P^2-pyrophosphate; a small amount of thymidine was also produced in the latter case. Purified rattlesnake venom phosphodiesterase converted the synthetic dinucleotide smoothly into 2 mols. of thymidine-5′ phosphate, and when applied to thymidine-3′ thymidine-5′ phosphate it gave a mixture of thymidine and thymidine-5′ phosphate although the rate of hydrolysis was much slower in this case. The results of these experiments with purified enzymes which were kindly carried out by Dr. R. Markham are the same as those reported for the dinucleotides obtained in solution after digestion of deoxyribonucleic acids with deoxyribonuclease (Markham and Smith, *loc. cit.*; Sinsheimer, *loc. cit.*) and support the view that these hydrolysis products are indeed 3′ : 5′-linked dinucleotides.

The preparation of the dinucleotide (V) represents the first chemical synthesis of a dinucleotide containing the internucleotidic linkage characteristic of the nucleic acids. The methods employed for its preparation should, with some modification, be capable of extension to the synthesis of tri- and higher poly-nucleotides of known constitution, products which would be of value in further studies on the structure of deoxyribonucleic acids and the mechanism of their hydrolytic degradation. Further work in this direction will be reported later.

Experimental

The names used below for binuclear compounds are to be regarded as temporary expedients pending evolution of a comprehensive nomenclature.

Partial Deacetylation of 3′ : 5′-Di-O-acetylthymidine.—A solution of 3′ : 5′-di-*O*-acetylthymidine (11·3 g.) Michelson and Todd, *J.*, 1955, 816) in ethanol (1 l.) containing saturated methanolic ammonia (165 c.c.) was kept at room temperature for 9 hr., then evaporated under reduced pressure. The residual gum was separated into its four components by countercurrent distribution in an automatically operated 100-stage machine with ethyl acetate–water (100 transfers). Paper chromatography was used to determine the location of each product in the series of fractions obtained from the apparatus; the contents of appropriate fractions were then combined and evaporated and the products recrystallised. The results are summarised in the accompanying Table. All products were identified by m. p. and mixed m. p.

Peak fraction	Fractions combined	Product	Wt. (g.)	M. p.	Recryst. from
5	1—12	Thymidine	0·92	183°	MeOH
28	16—37	5′-*O*-Acetylthymidine	2·75	146	$COMe_2$–C_5H_{12}
45	38—60	3′-*O*-Acetylthymidine	1·95	176	"
85	70—95	3′ : 5′-Di-*O*-acetylthymidine	3·18	125	EtOH

5′-O-Acetylthymidine-3′ Benzyl Phosphite.—5′-*O*-Acetylthymidine (0·74 g., 1 mol.) in methyl cyanide (10 c.c.) was added to a solution of *O*-benzylphosphorous *OO*-diphenylphosphoric

anhydride [from 1 g. (2 mols.) of benzyl dihydrogen phosphite] (Corby, Kenner, and Todd, *J.*, 1953, 3669) in dry benzene (20 c.c.). 2 : 6-Lutidine (0·66 c.c., 2 mols.) was added and the mixture set aside at room temperature overnight, moisture being excluded. Solvents were removed under reduced pressure, the residual clear gum was dissolved in chloroform, and the solution washed with water, sodium hydrogen carbonate, potassium hydrogen sulphate, and again water, then dried (Na_2SO_4). The dried solution was concentrated to small bulk and *cyclo*hexane was added. The precipitated *phosphite* was purified by redissolving it in chloroform and again precipitating it with *cyclo*hexane; dried *in vacuo* it formed a glassy foam (1·06 g.) (Found, in material dried at room temp./10^{-6} mm.: C, 51·4; H, 5·7; N, 5·9. $C_{19}H_{23}O_9N_2P$ requires C, 52·0; H, 5·3; N, 6·4%). On ascending chromatograms [Whatman No. 1; *n*-butanol–water (86 : 14)] the product had R_F 0·66. The phosphite decomposed slowly at room temperature.

Thymidine-3′ Thymidine-5′ Phosphate and Di(thymidine-3′) P¹P²-Pyrophosphate.—*N*-Chlorosuccinimide (0·49 g.) was added to a solution of 5′-*O*-acetylthymidine-3′ benzyl phosphite (1·5 g.) in a mixture of dry benzene (10 c.c.) and methyl cyanide (2 c.c.). After 3 hr. at room temperature the mixture was added to a solution of 3′-*O*-acetylthymidine (1 g.) in methyl cyanide (12 c.c.) containing 2 : 6-lutidine (2 c.c., 5 mols.) and the whole was left at room temperature for 36 hr., moisture being excluded. The mixture was evaporated under reduced pressure, the last traces of 2 : 6-lutidine being removed at a pressure of 0·1 mm. The residue was heated in water (76 c.c.), ethanol (20 c.c.), and 0·4N-sulphuric acid (4 c.c.) under reflux for 1 hr. before being concentrated to half-volume under reduced pressure. Saturated aqueous barium hydroxide was added to pH 10, the mixture left for 20 hr. at room temperature, and then dilute sulphuric acid was added to neutrality. The hot suspension was filtered, the combined filtrate and aqueous washings were concentrated to small bulk under reduced pressure and brought to pH 7·8 with aqueous barium hydroxide, and ethanol (10 vols.) was added. The precipitated mixed barium salts were collected, washed with ethanol, then ether, and dried; paper chromatography indicated that they contained thymidine-3′ phosphate, di(thymidine-3′) *P¹P²*-pyrophosphate, and thymidine-3′ thymidine-5′ phosphate. The salts were dissolved in water (50 c.c.) and run on to a column of Dowex 2 resin (chloride form; 6·5 × 3 cm.). Elution with 0·01N-hydrochloric acid removed thymidine-3′ phosphate and the dinucleoside phosphate together; the dinucleoside pyrophosphate was then eluted with 0·1N-hydrochloric acid. Appropriate fractions were combined, neutralised with saturated aqueous calcium hydroxide, and concentrated to small bulk under reduced pressure and, after careful adjustment to pH 7·4 with calcium hydroxide, ethanol (50 c.c.) was added to precipitate the calcium salt as a white amorphous powder. The crude calcium salt of the dinucleoside pyrophosphate weighed 350 mg. and that of the mixed simple phosphate 850 mg.

Calcium di(thymidine-3′) pyrophosphate (cf. III). The crude calcium salt (300 mg.) was dissolved in water (10 c.c.), ethanol (15 c.c.) was added, and the mixture set aside at 0° for 3 hr., then centrifuged. The clear supernatant liquid was concentrated under reduced pressure to small bulk (1 c.c.), and ethanol (50 c.c.) was added. The *calcium salt* of the dinucleoside pyrophosphate separated as a white powder (125 mg.) which was collected, washed with ethanol and ether, and dried (Found, in air-dried material: C, 31·6; H, 4·5; N, 7·7; P, 8·3%; ratio N/P = 2·05, thymidine/P = 1·14. $C_{20}H_{26}O_{15}N_4P_2Ca,4H_2O$ requires C, 32·5; H, 4·6; N, 7·6; P, 8·4%; N/P = 2·0, thymidine/P = 1·0). In this, as in all other cases, thymidine/P ratios were determined by estimation of thymidine by ultraviolet absorption (using $\varepsilon = 9300$ at 267 mμ) in N/20-hydrochloric acid, phosphorus being determined in an aliquot part of the same solution.

Calcium thymidine-3′ thymidine-5′ phosphate (cf. II). The crude mixed calcium salts (800 mg.) were dissolved in water (10 c.c.), the solution was filtered, and ethanol (15 c.c.) added. The mixture was left for 3 hr. at room temperature and the precipitated *calcium thymidine-3′ phosphate* (200 mg.) was centrifuged off. The salt was purified by dissolving it in a minimum of cold water, filtering the solution, and boiling the filtrate; the salt separated as a white crystalline precipitate (Found, in air-dried material: C, 29·9; H, 4·3; N, 6·6; P, 7·4. $C_{10}H_{13}O_8N_2PCa,2H_2O$ requires C, 30·3; H, 4·3; N, 7·1; P, 7·8%).

The supernatant liquid left after removal of the calcium salt by centrifugation was concentrated to small bulk (1 c.c.) under reduced pressure, boiling ethanol (9 c.c.) was added, and the mixture poured into a stirred mixture of acetone (15 c.c.) and ethanol (15 c.c.). The white precipitate of *calcium thymidine-3′ thymidine-5′ phosphate* (495 mg.) was collected by centrifugation, washed with acetone, then ether, and dried [Found, in air-dried material: C, 34·6; H, 5·5; N, 8·1; P, 4·7%; ratio N/P = 3·82, thymidine/P = 1·97. $(C_{20}H_{26}O_{13}N_4P)_2Ca,12H_2O$ requires C, 35·6; H, 5·5; N, 8·3; P, 4·6%; N/P = 4·0, thymidine/P = 2·0].

Thymidine-5′ Dibenzyl Phosphate.—A solution of crude 3′-*O*-acetylthymidine-5′ dibenzyl

phosphate (3·3 g.) (Michelson and Todd, *J.*, 1953, 951) in ethanol (20 c.c.) was added to saturated methanolic ammonia (20 c.c.), and the mixture was left overnight at room temperature. The mixture was then evaporated under reduced pressure and the residue shaken with chloroform and water. The aqueous layer, which contained a little thymidine-5′ benzyl phosphate, was discarded, and the chloroform layer washed with a small quantity of water, dried (Na_2SO_4), and concentrated to small bulk. *cyclo*Hexane was added and the precipitated pale yellow gum was purified by again dissolving it in chloroform and reprecipitating it with *cyclo*hexane. Dried *in vacuo*, *thymidine-5′ dibenzyl phosphate* formed a solid foam (2·06 g.) (Found, in material dried at room temp./10^{-5} mm.: C, 57·3; H, 5·8; N, 5·3. $C_{34}H_{37}O_8N_2P$ requires C, 57·3; H, 5·4; N, 5·6%).

The Dinucleotide (V) *and Di(thymidine-5′ Phosphate)-3′ P*^{1}*P*^{2}*-Pyrophosphate* (IV).—A solution of thymidine-5′ dibenzyl phosphate (2 g.) in methyl cyanide (15 c.c.) containing 2 : 6-lutidine (1·05 c.c.) was added to *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride (from 1·55 g. of benzyl dihydrogen phosphite) dissolved in dry benzene (30 c.c.). The mixture was kept for 20 hr. at room temperature, then evaporated under reduced pressure to a viscous syrup. Chloroform (50 c.c.) was added and the solution washed successively with water, solutions of sodium hydrogen carbonate and of potassium hydrogen sulphate, and water, and dried (Na_2SO_4), then concentrated to small bulk. The crude thymidine 3′-(benzyl phosphite) 5′-(dibenzyl phosphate) was precipitated as a viscous gum (2·5 g.) by addition of *cyclo*hexane, then reprecipitated from chloroform with *cyclo*hexane and dried at room temperature/10^{-3} mm.; but on account of its instability it was not further purified.

The crude phosphite (2·48 g.) was treated in dry benzene (10 c.c.) and methyl cyanide (2 c.c.) with *N*-chlorosuccinimide (0·55 g.), and after 3 hr. at room temperature added to a solution of 3′-*O*-acetylthymidine (1·15 g.) in methyl cyanide (13 c.c.) containing 2 : 6-lutidine (2·3 c.c., 5 mols.). The mixture was kept at room temperature for 36 hr., moisture being excluded. Solvents were removed under reduced pressure and the residue was refluxed in ethanol (22·5 c.c.), water (9 c.c.), and 0·4N-sulphuric acid (4·5 c.c.), then cooled to room temperature. Saturated aqueous barium hydroxide was added to pH 10, and the mixture left for 20 hr., then neutralised with dilute sulphuric acid. The precipitated barium salts were removed by filtration through Supercel, the combined filtrate and washings were concentrated to small bulk and adjusted to pH 7·8, and ethanol (10 vols.) was added. The precipitate was centrifuged off and dissolved in water (50 c.c.), and the solution brought to pH 4 with sulphuric acid. Barium sulphate was removed by centrifugation and the supernatant liquid and washings were shaken with hydrogen at room temperature and atmospheric pressure in presence of palladium oxide and palladised charcoal. When hydrogen uptake ceased, catalyst was removed, and the filtrate concentrated to 50 c.c. under reduced pressure and adjusted to pH 7·7 with barium hydroxide. The precipitated barium salt (A) was collected by centrifugation and worked up separately from the supernatant liquid (B).

(A) The precipitate was dissolved in a minimum of cold 0·1N-hydrochloric acid (*ca.* 3 c.c.), clarified by centrifugation, and poured into ethanol (2 vols.). The precipitated barium salt of the pyrophosphate (IV) (50 mg.) was contaminated with some inorganic phosphate which could not be separated from it but it contained no other nucleotidic material (Found, in air-dried material: C, 17·1; H, 2·8; N, 4·4; P, 11·6. Calc. for $C_{20}H_{26}O_{21}N_4P_4Ba_2,6H_2O$: C, 20·6; H, 3·3; N, 4·8; P, 10·7%).

(B) The aqueous supernatant liquid (B) (pH 7·7) was put on a column of Dowex 2 resin (chloride form; 6·5 × 2 cm.), the column washed with water, and the nucleotidic material eluted with 0·08N-hydrochloric acid, an automatic fraction collector being used. Appropriate fractions were combined, neutralised with aqueous calcium hydroxide, and taken to small volume under reduced pressure. Ethanol (100 c.c.) was added and the precipitated calcium salts (1·1 g.) were collected, washed with ethanol, then ether, and dried. Paper chromatography showed that the precipitate contained the salts of both thymidine-3′ : 5′ diphosphate and the desired dinucleotide (V), together with a trace of thymidine-5′ phosphate. The crude salt (1 g.) was therefore dissolved in cold water (50 c.c.) by prolonged shaking, and the solution boiled for 10 min., then filtered hot from the granular precipitate of *calcium thymidine-3′ : 5′ phosphate* (490 mg.) which was further purified by repeating its precipitation from aqueous solution by boiling (Found, in air-dried material: C, 22·4; H, 3·5; N, 5·3; P, 11·5. $C_{10}H_{13}O_{11}N_2P_2Ca_2,3H_2O$ requires C, 22·6; H, 3·4; N, 5·3; P, 11·6%).

The filtrate from the initial precipitation of the above salt was cooled and put on a column of Dowex 2 resin (chloride form; 5 × 1·5 cm.), the column cleared of mononucleotide by washing with 0·015N-hydrochloric acid, and the dinucleotide then eluted with 0·04N-hydrochloric acid.

Appropriate fractions were combined, neutralised with aqueous calcium hydroxide, concentrated to small bulk (*ca.* 10 c.c.) under reduced pressure, adjusted to pH 7·4 with calcium hydroxide, and filtered into ethanol (2 vols.). The white solid which separated was reprecipitated from ethanol as a granular powder (360 mg.). Recrystallised from water, the *calcium salt* of the dinucleotide (V) formed clusters of colourless prismatic needles, $[\alpha]_D^{20}$ 7·0° (*c*, 1·7 in H_2O) [Found, in air-dried material: C, 29·3; H, 4·6; N, 6·5; P, 8·0. $(C_{20}H_{28}O_{15}N_4P_2)_2Ca_3.14H_2O$ requires C, 29·7; H, 4·8; N, 6·9; P, 7·7. Found, in material dried for 12 hr. at 110°/1 mm.: P, 8·8. $(C_{20}H_{26}O_{15}N_4P_2)_2Ca_3$ requires P, 9·1%).

Characterisation of Thymidine Nucleotides and Related Compounds.—For abbreviations in the Table, see p. 2633.

(a) *Paper chromatography.* R_P values are given for ascending chromatograms on Whatman No. 1 paper with (A) *iso*propanol–water–ammonia (7 : 2 : 1) and (B) *n*-propanol–2N-hydrochloric acid (3 : 1).

(b) *Paper electrophoresis.* Experiments run for 12 hr. at 150 v on Whatman No. 1 paper in (i) 0·1M-disodium hydrogen phosphate and (ii) 0·1M-potassium dihydrogen phosphate. Movement towards the anode in all cases measured in cm. from a central base line.

(c) *Ultraviolet absorption.* Spectra of all compounds examined showed identical positions of maximum and minimum in N/50-hydrochloric acid ($\lambda_{max.}$ 267 mμ; $\lambda_{min.}$ 235 mμ) and in N/50-sodium hydroxide ($\lambda_{max.}$ 267 mμ; $\lambda_{min.}$ 245 mμ). The optical density ratio at 280/260 mμ was determined in each case.

	R_P values		Electrophoresis (cm.)		Optical density ratio 280/260 mμ	
	A	B	Na_2HPO_4	KH_2PO_4	N/50-HCl	N/50-NaOH
T3′–P	0·075	0·78	6·8	7·2	0·675	0·660
T5′–P	0·068	0·69	6·8	7·2	0·710	0·695
P–3′T5′–P	0	0·76	10·4	11·8	0·675	0·685
T3′–P–5′T	0·28	0·59	2·4	5·1	0·675	0·625
T3′–P–P–3′T	0·16	0·47	4·8	9·1	0·685	0·650
T5′–P–3′T5′–P	0·034	0·54	6·8	9·1	0·690	0·660
P–5′T3′–P–P–3′T5′–P ...	0	0·51	9·8	14·1	0·690	0·645

Enzyme Experiments.—Experiments using rattlesnake venom (*C. atrox*) were carried out according to Michelson and Todd (*J.*, 1953, 951). The crude prostatic phosphatase was prepared as a freeze-dried extract by the method of Beale, Harris, and Roe (*J.*, 1950, 1397); the thymidine derivative (*ca.* 1 mg.) was added to 0·1M-ammonium citrate (0·3 c.c.; pH 5) and the enzyme (0·1 c.c. of a solution containing 100 mg. of freeze-dried extract per 5 c.c.), and the mixture was incubated for 3 hr. at 37°.

In all enzyme experiments the products of reaction were identified by paper chromatography in 3 solvent systems [A and B above, and *n*-butanol–water (86 : 14)] and by paper electrophoresis as above.

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Triterpenoids. Part XX. The Constitution and Stereochemistry of a Novel Tetracyclic Triterpenoid.*

By D. H. R. Barton and K. H. Overton.

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The constitution and stereochemistry of the triterpenoid α-onoceradienediol (α-onocerin), obtained from the roots of *Ononis spinosa*, have been elucidated. α-Onoceradienediol has the molecular formula $C_{30}H_{50}O_2$, containing two secondary hydroxyl groups and two exocyclic methylene groups. It must, therefore, be tetracyclic. Removal of *either* of the secondary hydroxyl groups affords the *same* deoxy-compound and demonstrates the unique symmetry of the molecule.

The secondary hydroxyl groups have been proved to be contained in the system $\cdot CH_2 \cdot CH_2 \cdot CH(OH) \cdot CMe_2 \cdot$ in a six-membered ring, and the exocyclic methylene groups to be attached as part of the system $CH_2 \cdot C(:CH_2) - \overset{|}{C}H -$ in a six-membered ring.

Dehydrogenation of α-onoceradiene affords 1 : 2 : 5-trimethylnaphthalene in high yield. Ozonolysis of α-onoceradienediol diacetate followed by hydrolysis and oxidation gives a C_{24} tetraketone which on Wolff–Kishner reduction and then dehydrogenation furnishes 1 : 5-dimethylnaphthalene.

Acid-catalysed cyclisation of α-onoceradienediol affords a new series of symmetrical pentacyclic triterpenoids.

Based on these and other experiments the constitution and stereochemistry (I; R = OH) are proposed for α-onoceradienediol. This molecule is thus the first squalenoid to be detected in the vegetable kingdom; it is of importance in formulating theories of triterpenoid biogenesis.

The triterpenoid, α-onoceradienediol,† was first isolated a hundred years ago, from the roots of *Ononis spinosa* L. (the restharrow) by Hlasiwetz (*J. prakt. Chem.*, 1855, **65**, 419). Since that time its constitution has been studied in a desultory fashion, the earlier work being summarised in Elsevier's "Encyclopaedia" (Vol. XIV and supplement thereto). It has been established that α-onoceradienediol is a disecondary glycol containing two exocyclic methylene groups (or their equivalent) and having the composition $C_{30}H_{48}O_2$ or $C_{30}H_{50}O_2$. The more significant of the earlier work is that of Schulze (*Z. physiol. Chem.*, 1936, **238**, 35), who obtained 1 : 2 : 5 : 6-tetramethylnaphthalene by dehydrogenation of α-onoceradienediol, and that of J. Zimmermann (*Helv. Chim. Acta*, 1938, **21**, 853; 1940, **23**, 1110) to which more detailed reference is made below. In most respects we have had no difficulty in confirming this earlier work of Schulze and Zimmermann.

Extraction of commercial *Ononis* root gave α-onoceradienediol, conveniently isolated as its diacetate, by the procedure outlined on p. 2645, in about 0·2% yield. We express our best thanks to Messrs. Glaxo Laboratories for carrying out this extraction on a large scale. The first objective was to distinguish between the formulæ $C_{30}H_{48}O_2$ and $C_{30}H_{50}O_2$. This was done by studying the hydrogenation of the diacetate in acetic acid solution using a platinum catalyst. Zimmermann (*loc. cit.*) had reported that this afforded two onoceranediol diacetates. By thorough chromatographic fractionation of the hydrogenation product (see p. 2646) we were able to show that *three* onoceranediol diacetates were in fact produced. Onoceranediol-I diacetate, characterised by its sparing solubility, and onoceranediol-II diacetate, conveniently separated as the corresponding dibenzoate, had

* Part XIX, *J.*, 1954, 3689.

† This compound has been named onocerin or α-onocerin in the earlier literature. The solution of the structural problem, provided by the present paper, makes it opportune to put the nomenclature of the compound and its derivatives on a more systematic basis. By analogy with β-amyrenol or oleanenol for β-amyrin, we propose that α-onocerin should become α-onoceradienediol, being regarded as a derivative of the saturated tetracyclic hydrocarbon onocerane, $C_{30}H_{54}$. The naming of derivatives then follows logically.

properties in agreement with those recorded by Zimmermann. The third isomer, onoceranediol-III diacetate, further characterised as the diol, was not isolated by Zimmermann. All three onoceranediols were converted into the corresponding diketones and then, by Wolff–Kishner reduction, into the saturated onoceranes, none of which was identical with a known compound. The analytical data, particularly on the onoceranes, left no doubt that the correct molecular formula for α-onoceradienediol was $C_{30}H_{50}O_2$. The molecule must therefore be tetracyclic.

α-Onoceradienediol diacetate showed bands in the infrared spectrum at 1735 and 1240 cm.$^{-1}$ of a strength indicative of two acetate residues. The presence of two exocylic methylene groups was shown by the strength of the band at 890 cm.$^{-1}$. Other bands characteristic of exocylic methylene were present at 3110 and 1643 cm.$^{-1}$. Oxidation of α-onoceradienediol gave the known α-onoceradienedione. This compound showed no high-intensity ultraviolet absorption; the infrared spectrum exhibited bands at 1708 cm.$^{-1}$ (six-ring or aliphatic ketone; strength of band indicative of two such chromophores) and at 3100, 1642, and 892 cm.$^{-1}$ (exocyclic methylene group; strength of 892 cm.$^{-1}$ band indicative of two such chromophores). Finally ozonolysis of α-onoceradienediol diacetate afforded, in agreement with Zimmermann (*loc. cit.*), a bisnordioxo-onoceranediol diacetate in excellent yield, thus confirming chemically the presence of the two exocyclic methylene groups.

Wolff–Kishner reduction of α-onoceradienedione furnished α-onoceradiene which was not identical with any known compound. The infrared spectrum, taken in carbon tetrachloride solution, showed bands at 1390 and 1365 cm.$^{-1}$ indicative of *gem*-dimethyl groupings and at 1642 and 885 cm.$^{-1}$ (exocyclic methylene groups; strength of 885 cm.$^{-1}$ band indicative of two such groupings).

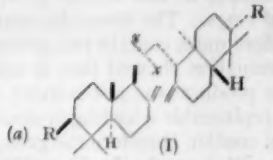
Acid-catalysed isomeration of α-onoceradienediol or its derivatives under fairly mild conditions affords compounds of the β-series (Zimmermann, *loc. cit.*) which are also diethylenic and therefore (see above) tetracyclic. According to Zimmermann (*loc. cit.*) ozonolysis of β-onoceradienediol diacetate gives acetone. In spite of numerous experiments we are unable to confirm this observation. Furthermore treatment of β-onoceradienediol diacetate with osmium tetroxide and reduction of the resultant complex with lithium aluminium hydride (cf. Barton, Ives, and Thomas, *J.*, 1954, 903) afforded an onocerane-hexaol which gave no trace of acetone on treatment with lead tetra-acetate. We conclude therefore that, contrary to the views of Zimmermann (*loc. cit.*), β-onoceradienediol does *not* contain an *iso*propylidene group.

The known β-onoceradienedione was prepared either by oxidation of β-onoceradienediol or, in a better state of purity, by acid-catalysed isomerisation of α-onoceradienedione. The ultraviolet spectrum of β-onoceradienedione showed no conjugation of the ethylenic linkages with each other or with the carbonyl groups. The infrared spectrum of β-onoceradienediol diacetate showed bands at 1730 and 1240 cm.$^{-1}$ (acetate; strength of band indicative of two such residues) but the bands characteristic of the exocyclic methylene groups (see above) had disappeared. Hydrogenation of β-onoceradienediol diacetate in acetic acid solution over a platinum catalyst gave onoceranediol-I diacetate (see above), thus showing that the transformation of the α- to the β-series very probably did not involve any skeletal rearrangement.

With these facts established, and having regard to recent views (see further below) on the nature of triterpenoid biogenesis, it was possible to deduce a hypothetical formula (I; R = OH) for α-onoceradienediol which was subsequently confirmed in every detail. We set out below the evidence for our structural proposals.

One of the most striking properties of the structure (I; R = OH) is its complete symmetry about the *x* . . . . *x* axis. This was established rigidly by showing that both hydroxyl groups of α-onoceradienediol were structurally equivalent. For convenience of exposition these two hydroxyl groups are arbitrarily designated (*a*) and (*b*) (see I). Partial hydrolysis of α-onoceradienediol *ab*-diacetate gave, besides unchanged diacetate and α-onoceradienediol, *a*-acetoxy-β-onoceradiene-*b*-ol. This was oxidised by chromic acid to furnish *a*-acetoxy-β-onoceradien-*b*-one, Wolff–Kishner reduction of which afforded α-onoceradien-*a*-ol further characterised as its acetate. *a*-Acetoxy-α-onoceradiene-*b*-ol

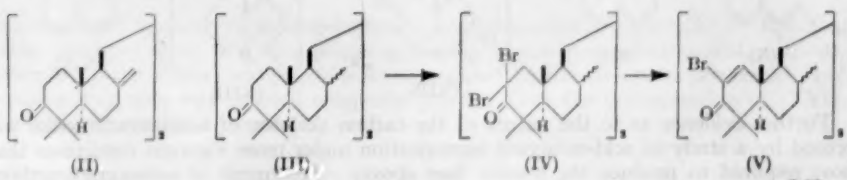
was also converted into the *a*-acetate *b*-benzoate which on partial hydrolysis gave *b*-benzoyloxy-α-onoceradien-*a*-ol. This, in turn, was oxidised to *b*-benzoyloxy-α-onoceradien-*a*-one. Wolff–Kishner reduction furnished α-onoceradien-*b*-ol, further characterised as the acetate. These compounds were identical with α-onoceradien-*a*-ol and its acetate (see above). Furthermore, hydrolysis of *a*-acetoxy-α-onoceradien-*b*-one gave the corresponding alcohol and thence *a*-benzoyloxy-α-onoceradien-*b*-one, identical in all respects, including the infrared spectrum, with the *b*-benzoyloxy-α-onoceradien-*a*-one referred to above.



(I)

The unique symmetry of (I; R = OH) also explains why only *three* onocerane derivatives are obtained on catalytic hydrogenation of (I; R = OAc) (see above). The two methyl groups produced by hydrogenation must be respectively equatorial-equatorial, axial-axial, equatorial-axial, and axial-equatorial. From the symmetrical structure (I) the last two stereoisomers would, of course, be identical.

The nature of the rings containing the hydroxyl groups of α-onoceradienediol was investigated as follows. α-Onoceradienedione (II) (see above) gave a positive Zimmermann test (W. Zimmermann, *Z. physiol. Chem.*, 1935, **233**, 257; 1936, **245**, 47; Barton and de Mayo, *J.*, 1954, 887; Broadbent and Klyne, *Biochem. J.*, 1954, **56**, xxx). In view of the symmetry, we take this as indicative of two CH_2·CO groups. In agreement bromination of onoceranedione-II (III) furnished a tetrabromo-dione (IV) which was resistant to further bromination. That the bromination was not accompanied by rearrangement was shown by reduction with zinc dust and acetic acid which gave back the parent onoceranedione-II. Treatment of tetrabromo-onoceranedione-II with collidine afforded the bismonobromo-enone (V), the absorptiom spectrum of which was indicative of the presence of *two* chromophores of the type (·CO·CBr:CH·) (Nussbaum, Mancera, Daniels, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 3263; Arya, Barton, and Cookson, unpublished observations). α-Onoceradienediol contains, therefore, two groupings of the type ·CH(OH)·CH_2·CH_2·.



(II) (III) (IV) (V)

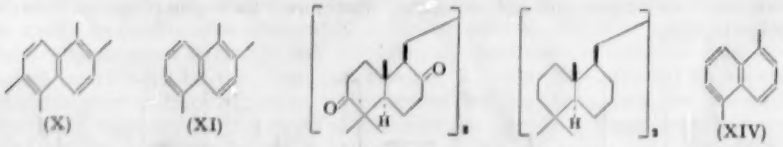
(VI) (VII) (IX) (VIII)

As mentioned above ozonolysis of α-onoceradienediol diacetate affords a diketone which must now be formulated as (VI; R = OAc). Alkaline hydrolysis gave the known (Zimmermann, *loc. cit.*) dihydroxy-diketone (VI; R = OH). On treatment with phosphorus pentachloride this diol underwent the usual dehydration with rearrangement to furnish the diketone (VII), the presence of two *iso*propylidene groups per mol. being demonstrated by ozonolysis which gave acetone, isolated as the 2 : 4-dinitrophenylhydrazone in 48% of the theoretical yield for two moles of acetone per mole of (VII): ozonolysis of *iso*lanosten-11-one (VIII) (Voser, White, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 830) under the same conditions gave 46% of acetone. The second product (IX) of the ozonolysis of the diketone (VII) could not be obtained

crystalline. These experiments prove the presence in α-onoceradienediol of two groupings ·CMe_2·CH(OH)·CH_2·CH_2· in six-membered rings.

The evidence outlined above characterises the two terminal rings of α-onoceradienediol. The other two rings were investigated in part as follows. It is clear that the two ketone groups of the diacetate (VI; R = OAc) cannot be contained in the terminal rings. They must therefore be present in the other two rings. The dione-diacetate (VI; R = OAc) showed bands at 1735 and 1240 (acetate; strength of band indicative of two acetates) and at 1710 $cm.^{-1}$. The 1710-$cm.^{-1}$ band was of a strength indicative of two ketone groups which, from the frequency, must be placed in six-membered rings. The dione-diacetate (VI; R = OAc) gave a positive Zimmermann test and therefore must contain two groupings of the type ·CH_2·CO·. In agreement, quantitative bromination showed that it consumed about five mols. of bromine. Although a crystalline product was not isolated it is clear, from the symmetry of the molecule, that at least six replaceable α-hydrogen atoms must be present. The second two rings of α-onoceradienediol contain therefore the grouping ·CH_2·C(:CH_2)·CH< in a six-membered ring in agreement with formula (I; R = OH).

Further evidence on the nature of the carbon skeleton of α-onoceradienediol was obtained by dehydrogenation. In agreement with Schulze's findings (*loc. cit.*) selenium dehydrogenation of α-onoceradienediol itself gave 1 : 2 : 5 : 6-tetramethylnaphthalene (X). However, selenium dehydrogenation of α-onoceradiene (I; R = H), where the possibility of a rearrangement of *gem*-dimethyl groups is minimised, afforded 1 : 2 : 5-trimethylnaphthalene (XI) in remarkably high yield [68% based on two moles of (XI) from one mole of (I; R = H)]. Proof of the position of attachment of the exocyclic methylene groups of α-onoceradienediol was obtained as follows. The dione-diol (VI; R = OH) was oxidised to the tetra-ketone (XII), which was also available by ozonolysis of α-onoceradienedione (II). This tetraketone was reduced by the Wolff–Kishner method to the hydrocarbon (XIII) which gave on dehydrogenation 1 : 5-dimethylnaphthalene (XIV) only.

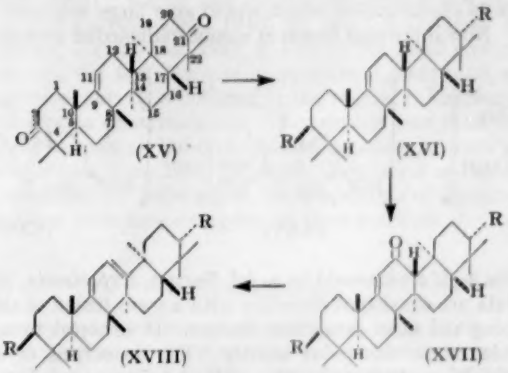


(X) (XI) (XII) (XIII) (XIV)

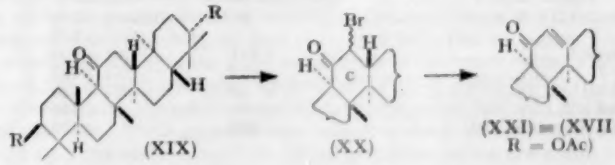
Further evidence as to the nature of the carbon skeleton of α-onoceradienediol was secured by a study of acid-catalysed isomerisation under more vigorous conditions than those required to produce the β-series (see above). Treatment of α-onoceradienedione (II) in benzene solution with acetic–sulphuric acid at room temperature (cf. Ames, Halsall, and Jones, *J.*, 1951, 450) gave a crystalline isomerisation product (XV) which we designate γ-onocerenedione. This diketone consumed per-acid at about the same rate as β-amyrin. Wolff–Kishner reduction afforded γ-onocerene (XVI; R = H). Similar acid-catalysed isomerisation of α-onoceradienediol diacetate afforded γ-onocerenediol diacetate (XVI; R = OAc), oxidised by chromic acid to the unsaturated ketone (XVII; R = OAc), $\lambda_{max.}$ 247 mμ (ε 9200) indicative of the chromophore (>C:CH·CO·) (see Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76). Reduction of this compound with lithium aluminium hydride followed by dehydration with toluene-*p*-sulphonic acid in acetic anhydride furnished a conjugated diene (XVIII; R = OAc). This contained the two ethylenic linkages in one ring, as shown by the ultraviolet absorption maximum at 281 mμ (ε 10,600) which is identical in position with that of analogous ring-C homoannular dienes in the α- and β-amyrin series.

That the γ-series of compounds contained only one ethylenic linkage, and therefore they were pentacyclic, was proved in the following way. Treatment of γ-onocerene (XVI; R = H) with hydrogen peroxide in acetic acid–chloroform gave a ketone (XIX; R = H) which was saturated to tetranitromethane. This ketone resisted Wolff–Kishner reduction under normal conditions, which is in agreement with the degree of steric

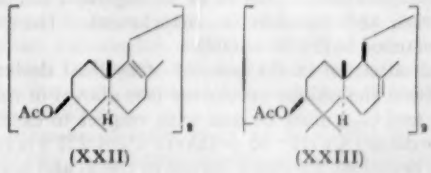
hindrance expected of such a carbonyl group (Barton and Holness, *J.*, 1952, **78**; Budziarek, Johnston, Manson, and Spring, *J.*, 1951, 3019; Barton, *J.*, 1953, 1027). In a similar manner γ-onocerenediol diacetate was converted into the corresponding saturated ketone



(XIX; R = OAc). This was smoothly brominated to the bromo-ketone (XX; R = OAc) which on dehydrobromination with collidine furnished an unsaturated ketone (XXI; R = OAc) which was identical with the ketone (XVII; R = OAc). The identity



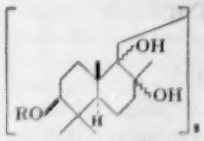
was confirmed by catalytic hydrogenation to γ-onocerenediol diacetate (XVI; R = OAc). These identities show that the unique symmetry of the α-onoceradienediol molecule is preserved in the γ-series and provides strong support for the structures proposed. It also explains why only one cyclised compound results, since the 9(11)-position of (XVI) is identical with the 12(13)-position.



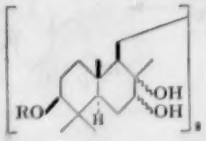
The final structural problem in the chemistry of α-onoceradienediol is the position of the ethylenic linkage in the β-series of compounds. β-Onoceradienediol diacetate must be represented by (XXII) or (XXIII), and the derived hexaol by (XXIV; R = H) or (XXV; R = H). In agreement with (XXIII), acetylation of the hexaol with pyridine and acetic anhydride gave a diacetate (XXV; R = Ac), which on oxidation with chromium trioxide rapidly consumed two atoms of oxygen. Further acetylation with acetic anhydride–sodium acetate gave a tetra-acetate (XXVI), or equivalent structure, as would be expected on the basis of (XXV). The placing of the ethylenic linkage in the β-series as in (XXIII) is somewhat unexpected (cf. Dietrich, E. Lederer, and Mercier, *Helv. Chim. Acta*, 1954, **37**, 705; Burn and Rigby, *Chem. and Ind.*, 1955, 386).

There remains for discussion the stereochemistry of α-onoceradienediol and its derivatives. Reduction of α-onoceradienedione (II) with sodium and propan-1-ol gave back

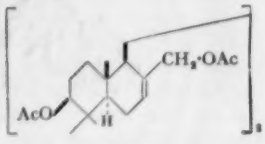
α-onoceradienediol in good yield. The two hydroxyl groups of the diol must, therefore, be equatorial. The molecular-rotation increments produced by acetylation of the hydroxyl groups of α-onoceradienediol and its derivatives are all positive (see Table). Such values are consistent with a 3β-configuration (Barton and Jones, *J.*, 1944, 659; Klyne and Stokes, *J.*, 1954, 1979), not a 3α-configuration which would give large negative Δ_1 values (Klyne and Stokes, *loc. cit.*). Now if the ring fusion in α-onoceradienediol were *trans* the equatorial



(XXIV)



(XXV)



(XXVI)

configuration would be β-, if *cis* it would be α- (cf. Barton, *Experientia*, 1950, **6**, 316). The molecular-rotation data are consistent therefore with a *trans*-fusion of rings, as in all other triterpenoids containing the same structural feature. It is hoped to advance more conclusive chemical evidence on this point shortly. The ozonolysis of α-onoceradienediol diacetate to furnish the bisnordione (VI; R = OAc) has been carried out under very mild

Parent alcohol	$[M]_D$ (in $CHCl_3$) Alcohol	Acetate	Δ_1 (per acetate residue)
α-Onoceradienediol (I; R = OH)	+ 80°	(mono) +121°	+ 41°
		(di) +147	+ 34
β-Onoceradienediol	+491	(di) +600	+ 55
Onoceranediol-II	+102	(di) +297	+ 98
Onoceranediol-III	+ 36	(di) +329	+147
α-Onoceradienol	+ 90	+140	+ 50
Bisnordionediol (VI; R = OH)	−303	−175	+ 64

conditions such as to minimise the danger of inversion of the connecting bridge at the centres adjacent to the newly formed ketone groups. The diketone formed was identical with that already described by Zimmermann (*loc. cit.*) (see above). Further, this diketone was not isomerised on vigorous treatment with base (see p. 2647). On these grounds we regard the connecting bridge of α-onoceradienediol as attached to the two bicyclic moieties in the more stable configuration. This is to be regarded (cf. Barton, *Chem. and Ind.*, 1953, 664) as equatorial, and therefore β-, attachment. The proposed stereochemistry has already been summarised in (I; R = OH).

The stereochemical situation in the γ-series of cyclised derivatives is simply derived. Since the molecules retain the unique symmetry (see above) of the parent α-series the two methyl groups at $C_{(8)}$ and $C_{(14)}$ must be *anti* with respect to each other. The very strong positive rotation of the diene (XVIII; R = OAc) ($[\alpha]_D$ +227°) is comparable with rotations recorded on numerous occasions for ring-C dienes in the α- and β-amyrin series and implies, in our opinion, a similar stereochemical environment. That is, the 8-methyl group must be β- and the 14-methyl group α-oriented. As already mentioned, the ketone (XIX; R = H) was not inverted at position 9, even on vigorous alkaline treatment: on conformational grounds then the configuration there must be α and therefore, on the basis of symmetry, the configuration at $C_{(13)}$ must be β. The proposed stereochemistry of the γ-series is therefore as already summarised in (XVI; R = OH) and derived formulæ. From the conformational point of view the compounds of the γ-series show a remarkable symmetry: this symmetry is reflected in the very high melting points of the γ-series of compounds. Indeed the symmetry of the α-onoceradienediol molecule itself also gives rise to m. p.s. which are anomalously high for tetracyclic compounds.

The absolute configuration of the α-onoceradienediol molecule is not defined by the above arguments, except that we consider that the high positive rotation of the ring-C

diene in the γ-series is indicative of a normal absolute configuration as depicted in (I; R = OH). Modern concepts of biogenesis (see below) are fully in accord with this view.

α-Onoceradienediol now takes its place, along with squalene (Heilbron *et al.*, *J.*, 1929, 873, 883, and earlier papers; Karrer and Helfenstein, *Helv. Chim. Acta*, 1931, **14**, 78) and ambrein (Ruzicka and Lardon, *ibid.*, 1946, **29**, 913; E. Lederer *et al.*, *ibid.*, p. 1354; E. Lederer and Mercier, *Experientia*, 1947, **3**, 188) in the small group of squalenoid triterpenoids. It represents the first tetracyclic squalenoid compound and, more important, the first representative of this class detected in the vegetable kingdom. In so far as recent concepts of the biogenesis of steroids and triterpenoids (see Ruzicka, *Experientia*, 1953, **9**, 357) place special emphasis on the cyclisation of squalene in ways which (see Woodward and Bloch, *J. Amer. Chem. Soc.*, 1953, **75**, 2023; Dauben *et al.*, *ibid.*, p. 3038; Ruzicka, *loc. cit.*) are not mechanistically self-evident, the elucidation of the constitution of α-onoceradienediol may be taken as welcome support for these concepts.

Experimental

For general experimental conditions see Part VII (*J.*, 1952, 2339). Rotations were determined in $CHCl_3$ solution unless otherwise specified. Ultraviolet absorption spectra were taken in EtOH solution with the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined by Messrs. Glaxo Laboratories in CS_2 solution unless stated to the contrary. Alumina for chromatography was Messrs. Peter Spence's Grade H; silica gel for the same purpose was obtained from Messrs. Hopkin and Williams Ltd. Light petroleum of b. p. 40—60° was used throughout unless stated to the contrary.

Extraction of α-Onoceradienediol (α-Onocerin).—Commercial *Ononis spinosa* root (1 kg.; small chips) was refluxed with 95% ethanol (3 l.) for 3 hr. The extraction was repeated with two further portions (3 l. each) of the same solvent. The combined extracts were concentrated *in vacuo* to about 500 ml. and potassium hydroxide (10 g.) in water (50 ml.) was added. After refluxing for a further hour the solution was diluted with water (500 ml.) and left at room temperature overnight. The crude onocerin was collected, dried at 100° (7—8 g.), suspended in dry pyridine (50 ml.) and acetic anhydride (25 ml.), and heated on the steam-bath for 30 min. (clear dark brown solution). On cooling, α-onoceradienediol diacetate (α-onocerin diacetate) separated. After being washed thoroughly with methanol this was filtered through alumina in 1 : 1 benzene–light petroleum. Crystallisation from chloroform–acetone gave pure α-onoceradienediol diacetate (1·35 g.) as well-formed rods, m. p. 222—224°, $[\alpha]_D$ +29° (*c* 3·84), +28° (*c* 1·74), $\lambda_{max.}$ 205 mμ (ε 9500), no selective absorption above 220 mμ (Found: C, 77·2, 77·2, 77·6, 77·65; H, 10·35, 10·45, 10·85, 10·75. Calc. for $C_{34}H_{54}O_4$: C, 77·5; H, 10·35%). Working up the pyridine–acetic anhydride mother-liquors in the same way gave a further quantity of α-onoceradienediol diacetate (860 mg.) of m. p. 216—218°. Grinding the *Ononis* root to a fine powder did not increase the yield of α-onoceradienediol diacetate. Hydrolysis of the diacetate with potassium hydroxide (6%) in 1 : 1 dioxan–methanol gave α-onoceradienediol. Recrystallised from chloroform–methanol, this had m. p. 202—203°, $[\alpha]_D$ +18° (*c* 0·287; 4-dm. tube), +1° (*c*, 0·92 in pyridine).

α-Onoceradienedione.—α-Onoceradienediol (1·42 g.) in "AnalaR" benzene (50 ml.) and "AnalaR" acetic acid (150 ml.) was treated with chromium trioxide (465 mg.) in 95% aqueous acetic acid (10 ml.) overnight at room temperature. After addition of methanol, the solution was concentrated to half its volume and diluted with water on the steam-bath until crystallisation commenced. Filtration afforded α-onoceradienedione (1·12 g.), m. p. (from chloroform–methanol) 183—185°, $[\alpha]_D$ −2° (*c* 2·31), −2° (*c* 1·61), unchanged on further recrystallisation and on chromatography. The diketone gave a strongly positive Zimmermann reaction. Reduction of α-onoceradienedione (50 mg.) with sodium–propanol under reflux for 2 hr. gave back α-onoceradienediol (m. p. and mixed m. p.) in almost quantitative yield. The identity was confirmed by conversion into the diacetate {m. p., mixed m. p., and rotation, $[\alpha]_D$ +29° (*c* 1·03)}.

α-Onoceradiene.—α-Onoceradienedione (200 mg.) was heated at 180° for 18 hr. with anhydrous hydrazine (1·0 ml.) and ethanol (5 ml.) containing dissolved sodium (400 mg.). Working up in the usual way and crystallisation from chloroform–methanol gave *α-onoceradiene*, m. p. 195—197°, $[\alpha]_D$ +29° (*c* 2·27 or 1·13) (Found: C, 87·6; H, 12·5. $C_{30}H_{50}$ requires C, 87·75;

H, 12·25%). The hydrocarbon was more conveniently obtained by the Wolff–Kishner reduction procedure of Barton, Ives, and Thomas (*J.*, 1955, 2056). α-Onoceradienedione (8·0 g.) in diethylene glycol (250 ml.; redistilled) containing dissolved sodium (5·0 g.) was treated with anhydrous hydrazine in the usual way (Barton, Ives, and Thomas, *loc. cit.*). Working up and filtration in light petroleum through alumina gave α-onoceradiene (4·3 g.).

Hydrogenation of α-Onoceradienediol Diacetate.—The diacetate (2·0 g.) in ethyl acetate (150 ml.) was hydrogenated overnight with a platinum catalyst (500 mg.) until the solution was saturated to tetranitromethane. Crystallisation from benzene–methanol afforded onoceranediol-I diacetate (190 mg.), m. p. 216—218°, $[\alpha]_D$ +55° (*c* 1·38) (Found : C, 77·0; H, 11·0. Calc. for $C_{34}H_{56}O_4$: C, 76·95; H, 11·0%). Hydrolysis of this diacetate (250 mg.) with dioxan–methanolic potassium hydroxide afforded onoceranediol-I (212 mg.), m. p. (from aqueous methanol) 259—263°. For these two compounds Zimmermann (*Helv. Chim. Acta*, 1938, **21**, 853) recorded m. p. 218°, $[\alpha]_D$ +57°, and m. p. 255° respectively.

After removal of the onoceranediol-I diacetate the combined mother-liquors were evaporated to dryness *in vacuo* and the residue carefully chromatographed on alumina (60 g.) in light petroleum. The column was eluted by gradually increasing the content of benzene in the eluant from 0 to 100% (26 fractions). Fractions 24—26 inclusive, eluted with pure benzene, gave (from chloroform–methanol) onoceranediol-I diacetate (127 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +55° (*c* 1·73)}. Fractions 4—8 inclusive, eluted with 15% benzene–light petroleum, were combined (320 mg.) and rechromatographed over alumina (15 g.), with elution as before (23 fractions). Crystallisation of the later fractions, eluted with 50% benzene–light petroleum, gave *onoceranediol-III diacetate* (250 mg.), long needles (from methanol), m. p. 150—151°, $[\alpha]_D$ +62° (*c* 1·53) (Found : C, 75·8; H, 11·05. $C_{34}H_{58}O_4.\frac{1}{2}MeOH$ requires C, 75·8; H, 11·0%). Hydrolysis with dioxan–methanolic potassium hydroxide afforded *onoceranediol-III*, long rods (from ethanol), m. p. 200—201°, $[\alpha]_D$ +8° (*c* 2·63 or 2·90) (Found : C, 80·1, 79·95; H, 11·85, 11·9. $C_{30}H_{54}O_2.\frac{1}{2}EtOH$ requires C, 79·5; H, 11·9%).

Careful examination of combined fractions 14—22 of the original chromatogram did not lead to a substance of authenticated homogeneity. The fractions were therefore combined (770 mg.) and hydrolysed with dioxan–methanolic potassium hydroxide, and the product was benzoylated with dry pyridine (5 ml.) and benzoyl chloride (1·54 ml.) overnight at room temperature. Crystallisation from methanol furnished *onoceranediol-II dibenzoate* (460 mg.), m. p. (plates) 200—201°, $[\alpha]_D$ +54° (*c* 3·44) (Found : C, 80·45; H, 9·5. $C_{44}H_{62}O_4$ requires C, 80·7; H, 9·55%). Hydrolysis in the usual way gave onoceranediol-II, m. p. 176—177° (from aqueous methanol and after drying overnight at 95° under 0·5 mm.), $[\alpha]_D$ +23° (*c* 1·98) (Found : C, 80·2; H, 12·0. Calc. for $C_{30}H_{54}O_2$: C, 80·65; H, 12·2%). Acetylation with pyridine–acetic anhydride at room temperature overnight furnished the diacetate, m. p. 171—172° (from chloroform–methanol), $[\alpha]_D$ +56° (*c* 3·22 or 1·54) (Found : C, 76·8; H, 10·9. Calc. for $C_{34}H_{58}O_4$: C, 76·95; H, 11·0%). For these two compounds Zimmermann (*loc. cit.*) recorded m. p. 187° and m. p. 170°, $[\alpha]_D$ +55°, respectively.

Onocerane-I.—Onoceranediol-I (200 mg.) in " AnalaR " acetic acid (10 ml.) and " AnalaR " benzene (10 ml.) was treated with chromium trioxide (100 mg.) in 95% aqueous acetic acid (10 ml.) added dropwise with stirring at room temperature. Filtration of the product in benzene through alumina and crystallisation from chloroform–ethanol, afforded onoceranedione-I, m. p. 212—213°, $[\alpha]_D$ +67° (*c* 1·57). For this compound Zimmermann (*loc. cit.*) recorded m. p. 209—211°. Onoceranedione-I (120 mg.) was heated at 180° for 16 hr. in anhydrous hydrazine (1·0 ml.) and ethanol (2·5 ml.) containing dissolved sodium (200 mg.). Filtration of the product through alumina in light petroleum solution gave *onocerane-I* (63 mg.), m. p. (from chloroform–methanol) 232—235° (evacuated capillary), 234—235° (Köfler block), $[\alpha]_D$ +51° (*c* 1·61) (Found : C, 86·7; H, 12·9. $C_{30}H_{54}$ requires C, 86·9; H, 13·1%).

Onocerane-II.—Onoceranediol-II (245 mg.) in " AnalaR " acetic acid (15 ml.) was treated with chromium trioxide (95 mg.) in 95% aqueous acetic acid (10 ml.) at room temperature for 48 hr. Filtration of the product in benzene through alumina and crystallisation from chloroform–methanol afforded onoceranedione-II, m. p. 160—162°, $[\alpha]_D$ +23° (*c* 1·20) (Found : C, 81·3; H, 11·05. Calc. for $C_{30}H_{56}O_2$: C, 81·4; H, 11·35%). Zimmermann (*loc. cit.*) recorded m. p. 154°. The diketone (140 mg.) was heated with anhydrous hydrazine (1·0 ml.) and ethanol (2·5 ml.) containing dissolved sodium (200 mg.) at 180° for 18 hr. After filtration of the product, in light petroleum through alumina, crystallisation from ethanol furnished *onocerane-II*, m. p. 135—136°, $[\alpha]_D$ +33° (*c* 2·95), +32° (*c* 1·15) (Found : C, 86·6; H, 12·9%).

Onocerane-III.—Onoceradienediol-III (120 mg.) in " AnalaR " acetic acid (3 ml.) and " AnalaR " benzene (2·5 ml.) was treated with chromium trioxide (50 mg.) in water (1·0 ml.)

overnight at room temperature. Crystallisation of the product from aqueous ethanol afforded onoceranedione-III, plates, m. p. 168—169°, $[\alpha]_D$ −6° (*c* 1·64) (Found: C, 81·2; H, 11·3%). The diketone (75 mg.) was heated with 100% hydrazine hydrate (0·6 ml.) and ethanol (2·5 ml.) containing dissolved sodium (150 mg.) at 180° for 16 hr. Filtration of the product through alumina in light petroleum solution and crystallisation from ethanol afforded *onocerane-III*, m. p. (needles) 123—124°, $[\alpha]_D$ +12° (*c*, 1·75) (Found: C, 86·9; H, 13·05%).

β-Onoceradienediol (β-Onocerin) and its Derivatives.—α-Onoceradienediol diacetate (1·0 g.) in acetic acid (200 ml.) was treated with concentrated sulphuric acid (2·0 ml.) in the same solvent (50 ml.) at 40° for 3 hr. Crystallisation from benzene–methanol afforded β-onoceradienediol diacetate (435 mg.), m. p. 231—236° (changes from plates to needles), 261—264° (evacuated capillary after drying for 45 min. at 110°/0·1 mm.), $[\alpha]_D$ +114° (*c* 1·89), +113° (*c* 1·24). Zimmermann (*Helv. Chim. Acta*, 1938, **21**, 853) gives m. p. 260° $[\alpha]_D$ +106°.

β-Onoceradienediol diacetate (200 mg.) was hydrolysed with potassium hydroxide (3·0 g.) in dioxan (15 ml.) and methanol (35 ml.) under reflux for 2 hr. Dilution with water gave β-onoceradienediol, m. p. 233—236° (from aqueous–methanol), $[\alpha]_D$ +111° (*c* 1·95) (157 mg.). This was taken up in " AnalaR " acetic acid (10 ml.) and treated with chromium trioxide (50 mg.) in 95% aqueous acid (3·0 ml.) at room temperature for 48 hr. Crystallisation of the product from methanol gave somewhat impure β-onoceradienedione, needles, m. p. 162—164°, $[\alpha]_D$ +166° (*c* 1·19), $\lambda_{max.}$ 245 mμ (ε 2600). Contamination with αβ-unsaturated ketone is clearly indicated. A more satisfactory specimen of the β-diketone was prepared as follows. α-Onoceradienedione (200 mg.) was refluxed with acetic acid–concentrated hydrochloric acid (9 : 1; 50 ml.) for 18 hr. Chromatography of the product over alumina and crystallisation from methanol gave pure β-onoceradienedione (32 mg.), m. p. 168—170°, $[\alpha]_D$ +187° (*c* 0·94). Zimmermann (*loc. cit.*) recorded m. p. 170°.

Hydrogenation of β-Onoceradienediol Diacetate.—The diacetate (325 mg.) was hydrogenated in " AnalaR " acetic acid with a platinum catalyst for 2 days. The product was chromatographed over alumina (8·0 g.) in 1 : 1 light petroleum–benzene (five fractions). All but the first fraction consisted of pure onoceranediol-I diacetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +49° (*c* 2·02)}.

Ozonolysis of α-Onoceradienediol Diacetate.—α-Onoceradienediol diacetate (3·0 g.) in dry methylene chloride (50 ml.) was cooled to −70° and ozonised until a test portion was negative to tetranitromethane. Acetic acid (25 ml.) was added and zinc dust (5 g.) was stirred in portionwise during 2 hr., the temperature being held at −20°. Crystallisation from aqueous ethanol afforded diacetoxydinoronoceranedione (VI; R = OAc) (2·11 g.), m. p. 120—125° (resolidified) and 162—164°, $[\alpha]_D$ −33° (*c*, 3·56, 2·42, or 1·15), $\lambda_{max.}$ 286 mμ (ε 75). After drying at 100/0·1 mm. for 14 hr. the compound melted at 164—166°.

The diketone diacetate (VI; R = OAc) (350 mg.) was refluxed with 5% methanolic potassium hydroxide solution (25 ml.) for 2 hr. Crystallisation of the product from benzene–light petroleum (b. p. 60—80°) gave the dihydroxy-diketone (VI; R = OH), rods, m. p. 216—218°, $[\alpha]_D$ −68° (*c* 2·40). For this compound and for its parent diacetate (see above) Zimmermann (*Helv. Chim. Acta*, 1940, **23**, 1110) recorded m. p. 217° and 165° respectively.

In further experiments the diketone diacetate (350 mg.) was refluxed (*a*) with 10% methanolic potassium hydroxide overnight and (*b*) with 20% methanolic potassium hydroxide for 3 hr. In both cases the same dihydroxy-diketone was formed. Reacetylation with pyridine–acetic anhydride at room temperature overnight gave back the parent diketone diacetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ −34° (*c* 1·37)}.

The diketone gave an immediate response in the Zimmermann colour reaction.

The diketone diacetate (107 mg.) in " AnalaR " acetic acid (11·7 ml.) was mixed with a solution of bromine (256 mg.; 8 mols.) in " AnalaR " acetic acid (8·3 ml.) with addition of one drop of 50% hydrobromic–acetic acid. The consumption of bromine (in mols.) after the stated times (in parentheses) was as follows: 0·94 (20 min.), 2·03 (60 min.), 3·87 (90 min.) 4·44 (16 hr.), 4·78 (22 hr.), 4·91 (44 hr.). A duplicate experiment with a higher concentration of hydrobromic acid as catalyst led to an uptake of 4·90 mols. of bromine in 75 min.

Formation of the Tetraketone (XII).—(*a*) The dihydroxy-diketone (VI; R = OH) (82 mg.) in " AnalaR " acetic acid (3·0 ml.) was treated overnight at room temperature with chromium trioxide (30 mg.) in the same solvent (6·0 ml.). Crystallisation of the product from methanol furnished the *dinoronoceranetetraone* (XII), stout rods, m. p. 196—198°, $[\alpha]_D$ −104° (*c* 2·45) (Found: C, 75·7; H, 9·35. $C_{28}H_{42}O_4$ requires C, 75·95; H, 9·55%).

(*b*) α-Onoceradienedione (500 mg.) in methylene dichloride (50 ml.) was ozonised at −70° until a test portion was negative to tetranitromethane. After working up with acetic

acid and zinc dust as outlined above, filtration of the product in benzene through alumina gave the same tetraketone (417 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ −106° (*c* 2·57)}.

Action of Phosphorus Pentachloride on the Dihydroxy-diketone (VI; R = OH).—A solution of the dihydroxy-diketone (450 mg.) in " AnalaR " benzene (200 ml.) was concentrated to half its volume *in vacuo*. To this solution, cooled to 0°, there was added phosphorus pentachloride (700 mg.) in one portion with stirring. The stirring was continued with passage of a stream of dry oxygen-free nitrogen and exclusion of moisture for 30 min. (all phosphorus pentachloride in solution). Chromatography over alumina (15 g.) gave a crystalline *dinoronoceradienedione*, plates (from chloroform–methanol), m. p. 156—160°, $\lambda_{max.}$ 205 mμ (ε 17,500), $[\alpha]_D$ −113° (*c* 2·28), −112° (*c* 1·25) (Found : C, 81·9; H, 9·35. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%). Fractionation from chloroform–methanol did not alter the rather diffuse m. p.

Ozonolysis of the product (163 mg.) (obtained with phosphorus pentachloride) at −60° in methylene dichloride (10 ml.) and working up by addition of zinc dust and acetic acid as outlined above gave acetone. This was determined in the following way. The solution of acetone in methylene dichloride–acetic acid was distilled over into a solution of 2 : 4-dinitrophenylhydrazine (250 mg.) in ethanol (50 ml.) and concentrated hydrochloric acid (1·0 ml.). During the distillation ethanol was added to the original solution so that the final volume of the distillate was 200 ml. The solvent was removed from the distillate *in vacuo* and the residue chromatographed over alumina (5·0 g.) on benzene. Elution with benzene gave acetone 2 : 4-dinitrophenylhydrazone (84 mg., 48% based in two *iso*propylidene groups), identified by m. p., mixed m. p., and analysis (Found : C, 45·8; H, 4·45; N, 25·2, 22·9. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·25; N, 23·5%).

In another experiment the ozonolysis product was decomposed at low temperature with zinc dust and acetic acid. Careful chromatography of the product did not give any crystalline product.

In a model experiment *iso*lanosten-11-one (500 mg.), kindly provided by Mr. D. A. J. Ives, was ozonised in the same way to give acetone 2 : 4-dinitrophenylhydrazone (135 mg., 46%), identified by m. p. and mixed m. p.

Ozonolysis of β-Onoceradienediol Diacetate.—β-Onoceradienediol diacetate (135 mg.) was ozonised and the product worked up essentially as described above. In spite of extensive examination the formation of acetone, claimed by Zimmermann (*Helv. Chim. Acta*, 1940, **23**, 1110), could not be confirmed.

Hydroxylation of β-Onoceradienediol Diacetate with Osmium Tetroxide.—The diacetate (300 mg.) in dry pyridine (5 ml.) was treated with osmium tetroxide (375 mg.) in dry ether (5 ml.) in the dark for 5 days. Lithium aluminium hydride (600 mg.) in dry ether (20 ml.) was then added and the solution refluxed for 1 hr. The excess of lithium aluminium hydride was destroyed with ethyl acetate. Crystallisation of the product from methanol–benzene furnished the desired *onoceranehexaol* (XXV; R = H) (100 mg.), silky needles, m. p. 268—271° (evacuated capillary), $[\alpha]_D$ +20° (*c* 3·18) (Found : C, 70·0; H, 10·7. $C_{30}H_{54}O_6$ requires C, 70·55; H, 10·65%). The hexaol (95 mg.) in acetic acid (2 ml.) was treated with lead tetra-acetate (200 mg.) in acetic acid (10 ml.) for 18 hr. at room temperature. The solution was diluted with water (150 ml.) and distilled into a solution of 2 : 4-dinitrophenylhydrazine (250 mg.) in ethanol (50 ml.) and concentrated hydrochloric acid (1·0 ml.). The distillate was evaporated to dryness *in vacuo* and the residue chromatographed for acetone 2 : 4-dinitrophenylhydrazone (see above). None of this compound could be detected.

The hexaol (XXV; R = H) (230 mg.) was acetylated with pyridine–acetic anhydride overnight at room temperature, furnishing the diacetate (XXV; R = Ac), plates (from chloroform–methanol), m. p. 268—271° (evacuated capillary), $[\alpha]_D$ +37° (*c* 1·67) (Found : C, 68·60; H, 9·65. $C_{34}H_{58}O_8$ requires C, 68·65; H, 9·80%).

Further acetylation of the diacetate (110 mg.) in refluxing acetic anhydride (containing 5% of anhydrous sodium acetate) for 1 hr. afforded, after chromatography over alumina, the tetra-acetate (XXVI), rods (from methanol), m. p. 234—237° (evacuated capillary), $[\alpha]_D$ +21° (*c* 0·57) (Found : C, 70·95; H, 9·5; Ac, 24·3. $C_{38}H_{58}O_8$ requires C, 71·0; H, 9·1; Ac, 26·8%).

When the hexaol diacetate, after rigorous drying *in vacuo*, was treated with chromium trioxide (2·2 atom-equiv. of oxygen) in aqueous (2%) acetic acid at room temperature overnight, 2 atom-equivs. of oxygen were consumed rapidly. Neither the resulting diketone nor its dioxime could be obtained crystalline.

Treated with lead tetra-acetate in acetic acid at room temperature, the hexaol diacetate (XXV; R = Ac) consumed 2 mols. within 5 min., and no more during a further 19 hr.

Bromination of Onoceranedione-II.—The diketone (42 mg.) in " AnalaR " acetic acid (5 ml.) containing one drop of hydrobromic–acetic acid was treated dropwise with a solution of bromine in acetic acid (0·53% w/v) at 50°. Two mols. of bromine were rapidly absorbed, a further two mols. more slowly; there was no additional uptake after 2 hr. at the same temperature in the presence of a further 2 mols. of bromine. Crystallisation of the product from chloroform–methanol gave *tetrabromo-onoceranedione-II*, needles, m. p. 194—196° (decomp.), $[\alpha]_D$ −20° (*c* 2·90) (Found: C, 48·15; H, 6·2; Br, 43·05. $C_{30}H_{46}O_2Br_4$ requires C, 47·5; H, 6·1; Br, 42·15%). This tetrabromo-compound (15 mg.) in " AnalaR " acetic acid (1 ml.) was kept with a solution of bromine in acetic acid (5 ml.; 8·16 mg. per ml.) for 5 days at room temperature. Back-titration showed that less than 0·1 mol. of bromine had been consumed.

Tetrabromo-onoceranedione-II (20 mg.) in " AnalaR " acetic acid (3 ml.) was refluxed with zinc dust (150 mg.) for 2 hr. Crystallisation of the product from chloroform–methanol gave back onoceranedione-II (m. p. and mixed m. p.).

Tetrabromo-onoceranedione-II (210 mg.) in redistilled collidine (3 ml.) was heated in a sealed tube at 180° for 2 hr. Chromatography of the product over alumina (5 g.) in 10—50% benzene–light petroleum (six fractions) gave *bisdehydrodibromo-onoceranedione-II*, m. p. (from chloroform–methanol) 221—223°, $[\alpha]_D$ +34° (*c* 1·88), $\lambda_{max.}$ 255 mμ (ε 17,500) (Found: C, 60·65; H, 7·5; Br, 26·9. $C_{30}H_{44}O_2Br_2$ requires C, 60·4; H, 7·4; Br, 26·85%).

γ-Onocerenedione.—α-Onoceradienedione (3·0 g.) in " AnalaR " benzene (30 ml.) and 15 : 85 concentrated sulphuric acid–" AnalaR " acetic acid (300 ml.; mixed with cooling) was kept at room temperature for 3 days. After dilution with water, extraction with ether, and washing with sodium hydroxide solution, evaporation of the ethereal solution *in vacuo* and treatment of the residue with light petroleum (b. p. 60—80°) gave a crystalline product. This was filtered through alumina in benzene solution to furnish *γ-onocerenedione* (525 mg.), stout prisms (from benzene–light petroleum), m. p. 291—293° (evacuated capillary), $[\alpha]_D$ +104° (*c* 2·07) (Found: C, 81·8; H, 10·45. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·55%). In a further experiment the α-onoceradienedione was treated for only 15 hr. Chromatography of the product over alumina gave γ-onocerenedione and then β-onoceradienedione in a ratio of approximately 1 : 2.

γ-Onocerenedione reacted with ethereal monoperphthalic acid at 0°, consuming 34% of the theoretical amount for one ethylenic linkage in 4 days. A solution of β-amyrin benzoate of the same concentration treated in the same way consumed 29% in the same time.

γ-Onocerene.—γ-Onocerenedione (52 mg.) was heated with anhydrous hydrazine (0·5 ml.) and ethanol (2 ml.) containing dissolved sodium (100 mg.) at 180° for 20 hr. Filtration of the product in light petroleum through alumina gave *γ-onocerene*, rods (from methanol), m. p. 254—256° (Köfler block), $[\alpha]_D$ +83° (*c* 1·58) (Found: C, 87·65; H, 12·3. $C_{30}H_{50}$ requires C, 87·75; H, 12·3%).

γ-Onocerenediol Diacetate.—α-Onoceradienediol diacetate (250 mg.) in " AnalaR " benzene (2·5 ml.) and 15 : 85 concentrated sulphuric acid–" AnalaR " acetic acid (25 ml.) was kept at room temperature overnight. Chromatography of the product over alumina (8 g.) in light petroleum and elution with 30—100% benzene–light petroleum (six fractions) afforded *γ-onocerenediol diacetate*. Purified by vacuum-sublimation and crystallisation from chloroform–methanol this (27 mg.) had m. p. 333—336° (evacuated capillary), $[\alpha]_D$ +79° (*c* 1·55), +80° (*c* 1·45) (Found: C, 77·4; H, 10·5. $C_{34}H_{54}O_4$ requires C, 77·5; H, 10·35%).

Diacetoxy-γ-onocerenone.—γ-Onocerenediol diacetate (100 mg.) in refluxing " AnalaR " acetic acid (20 ml.) was treated with chromium trioxide (80 mg.) in 95% aqueous acetic acid (10 ml.) added dropwise during 1 hr. The refluxing was continued for a further hour. Filtration of the crude product in benzene through alumina and crystallisation from benzene–ethanol gave diacetoxy-γ-onocerenone, large hexagonal plates, m. p. 356—360° (evacuated capillary), $[\alpha]_D$ +86° (*c* 2·27), $\lambda_{max.}$ 247 mμ (ε 9200) (Found: C, 75·2; H, 9·8. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·7%).

γ-Onoceradienediol Diacetate.—Oxo-γ-onocerenediol diacetate (250 mg.) in anhydrous ether (30 ml.) was refluxed with lithium aluminium hydride (300 mg.) for 2 hr. Excess of lithium aluminium hydride was decomposed by addition of ethyl acetate, and the crude product, obtained in the usual way, refluxed with toluene-*p*-sulphonic acid (25 mg.) in acetic anhydride (5 ml.) for 1 hr. Crystallisation from chloroform–methanol afforded *γ-onoceradienediol diacetate*, m. p. 350—353° (evacuated capillary), $[\alpha]_D$ +221° (*c* 3·45), $\lambda_{max.}$ 281 mμ (ε 10,800) (Found: 77·75, 77·7; H, 9·55, 9·95. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%).

γ-Onoceranone.—γ-Onocerene (190 mg.) in " AnalaR " acetic acid (15 ml.) was heated on the steam-bath and treated with hydrogen peroxide (30%; 3 ml.) in " AnalaR " acetic acid

(3 ml.) added portionwise during 2·5 hr. A little chloroform was added from time to time to ensure a clear solution. Crystallisation of the product from chloroform–methanol gave *γ-onoceranone*, plates, m. p. 295—298°, $[\alpha]_D$ +25° (*c* 1·27) (Found: C, 82·75; H, 11·5. $C_{30}H_{50}O,\frac{1}{4}CH_4O$ requires C, 82·8; H, 11·85. Found, after drying at 120°/0·1 mm. for 5 days: C, 83·65; H, 12·2. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). This ketone (45 mg.) was recovered unchanged (m. p. and mixed m. p.) after being subjected to the normal sealed-tube Wolff–Kishner reduction conditions.

Transformations with γ-Onocerenediol Diacetate.—γ-Onocerenediol diacetate (200 mg.) in "AnalaR" acetic acid (15 ml.), heated on the steam-bath, was treated with hydrogen peroxide (30%; 3·5 ml.) in "AnalaR" acetic acid (3·5 ml.) added portionwise during 2·5 hr. A little chloroform was added from time to time to ensure a clear solution (internal temp. 85°). Crystallisation of the product from chloroform–methanol afforded *diacetoxy-γ-onoceranone*, hexagonal plates, m. p. >370°, $[\alpha]_D$ +32° (*c* 1·46), $\lambda_{max.}$ 296 mμ (ε 30) (Found: C, 75·15; H, 10·05. $C_{34}H_{54}O_5$ requires C, 75·25; H, 10·05%). The homogeneity of this compound was confirmed by chromatography.

Diacetoxy-γ-onoceranone (156 mg.) in "AnalaR" acetic acid (50 ml.) containing 2 drops of hydrobromic–acetic acid was treated at 75° with bromine in "AnalaR" acetic acid (5·87 ml.; 8·62 mg. of bromine per ml.; 1·1 mols.) added in ½-ml. portions as rapidly as it was consumed (2 hr.). Crystallisation of the product from chloroform–methanol afforded *bromodiacetoxy-γ-onoceranone*, rods, m. p. about 320° (decomp.), $[\alpha]_D$ +15° (*c* 1·60) (Found: C, 65·55; H, 8·65; Br, 13·2. $C_{34}H_{53}O_5Br$ requires C, 65·7; H, 8·6; Br, 12·9%).

The bromo-ketone (80 mg.) was heated with redistilled collidine (2 ml.) in a sealed tube at 180° for 1·5 hr. Crystallisation of the product from chloroform–ethanol gave diacetoxy-γ-onocerenone, identified by m. p., mixed m. p., absorption [$\lambda_{max.}$ 247 mμ (ε 9000)], and rotation {$[\alpha]_D$ +89° (*c* 1·63)}. The identity was further checked by hydrogenation of the unsaturated ketone (45 mg.) in "AnalaR" acetic acid over platinum at room temperature for 2 days. Crystallisation from chloroform–methanol gave γ-onocerenediol diacetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +73° (*c* 1·66)}.

Semihydrolysis of α-Onoceradienediol Diacetate.—α-Onoceradienediol diacetate (1·1 g.) in dioxan (25 ml.), water (10 ml.), and 40% aqueous dioxan (11·8 ml.) containing potassium hydroxide (9 mg. per ml.; 0·9 mole) was refluxed overnight. The addition of phenolphthalein showed that this time was required for the complete consumption of the potassium hydroxide. Chromatography of the product over alumina (30 g.) in benzene solution gave unchanged α-onoceradienediol diacetate (235 mg.), identified by m. p. and mixed m. p. Elution with 9 : 1 ether–methanol gave a mixture which was further chromatographed over silica gel (45 g.) in light petroleum. Elution with 9 : 1 light petroleum–benzene (four fractions) afforded *α-onoceradienediol monoacetate* (560 mg.), needles [from benzene–light petroleum (b. p. 60—80°)], m. p. 156—158°, $[\alpha]_D$ +25° (*c* 1·37), +26° (*c* 0·70) (Found: C, 79·1; H, 10·5. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). Elution with methanol gave a small amount of α-onoceradienediol (m. p. and mixed m. p.).

α-Onoceradienediol monoacetate (339 mg.) in "AnalaR" acetic acid (10 ml.) was treated with chromium trioxide (50 mg.) in 95% aqueous acetic acid (5 ml.) at room temperature overnight. Filtration of the product through alumina in benzene gave the *monoacetate ketone*, needles (from chloroform–methanol), m. p. 187—189°, $[\alpha]_D$ +18° (*c* 1·98) (Found: C, 78·6; H, 10·25. $C_{32}H_{50}O_3,\frac{1}{4}CH_4O$ requires C, 78·3; H, 10·5%).

α-Onoceradienediol monoacetate (700 mg.) in dry pyridine (5 ml.) and benzoyl chloride (0·7 ml.) was left overnight at room temperature. Chromatography of the product over alumina (20 g.) in light petroleum and elution with 1 : 10 benzene–light petroleum to pure benzene (10 fractions) gave *α-onoceradienediol acetate benzoate*, m. p. 133—135° (from chloroform–methanol), $[\alpha]_D$ +30° (*c* 1·39), $\lambda_{max.}$ 229 mμ (ε 15,500) (Found: C, 77·6; H, 9·5. $C_{39}H_{56}O_4,\frac{1}{2}CH_4O$ requires C, 77·4; H, 9·75%).

α-Onoceradienol.—(*a*) The monoacetate ketone (180 mg.) was heated with anhydrous hydrazine (0·9 ml.) in ethanol (4·5 ml.) containing dissolved sodium (350 mg.) at 180° for 14 hr. Crystallisation of the product from aqueous ethanol gave *α-onoceradienol*, fine needles, m. p. 182—184°, $[\alpha]_D$ +21° (*c* 1·70) (Found: C, 84·3; H, 12·0. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Acetylation with pyridine–acetic anhydride at room temperature furnished *α-onoceradienyl acetate*, needles (from chloroform–methanol), m. p. 141—143°, $[\alpha]_D$ +30° (*c* 1·52) (Found: C, 82·3; H, 11·5. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%).

(*b*) α-Onoceradienediol acetate benzoate (610 mg.) in dioxan (10 ml.) and 2 : 3 aqueous dioxan (6·7 ml.) containing potassium hydroxide (9 mg. per ml.; 1·0 mol.) was heated under

reflux for 16 hr. Chromatography of the product over alumina (20 g.) in benzene and elution with 1⟶4 : 10 ether–benzene gave *α-onoceradienediol monobenzoate*, rods (from chloroform methanol), m. p. 222—224°, $[\alpha]_D$ +25° (*c* 1·54), $\lambda_{max.}$ 229 mμ (ε 15,100) (Found : C, 81·1; H, 9·75. $C_{37}H_{54}O_3$ requires C, 81·25; H, 9·95%). Oxidation of this monobenzoate (233 mg.) in "AnalaR" acetic acid (20 ml.) with chromium trioxide (32 mg.) in 95% aqueous acetic acid (5 ml.) overnight at room temperature gave the *monobenzoate ketone*, needles (from methanol), m. p. 152—154°, $[\alpha]_D$ +23° (*c* 1·56) (Found : C, 81·5; H, 9·55. $C_{37}H_{52}O_3$ requires C, 81·55; H, 9·5%). This monobenzoate ketone (112 mg.) was heated with anhydrous hydrazine (1·0 ml.) and ethanol (3·0 ml.) containing dissolved sodium (200 mg.) at 180° for 14 hr. Crystallisation of the product from aqueous ethanol gave α-onoceradienol identical {m. p., mixed m. p., crystal form, and rotation, $[\alpha]_D$ +20° (*c* 2·11)} with material described under this name above. The identity was confirmed by acetylation to α-onoceradienyl acetate {m. p., mixed m. p., and rotation, $[\alpha]_D$ +29° (*c* 1·35)}.

Further Correlation of the Hydroxyl Groups of α-Onoceradienediol.—The monoacetate ketone from α-onoceradienediol (775 mg.) in dioxan (15 ml.) and 2 : 3 aqueous dioxan (11·35 ml.) containing potassium hydroxide (9 mg. per ml.; 1·1 mols.) was heated under reflux for 14 hr. The product was chromatographed over alumina (30 g.) in benzene. Elution with benzene gave unchanged monoacetate ketone (56 mg.) (m. p. and mixed m. p.). Elution with ether afforded the desired *hydroxyonoceradienone* (530 mg.), needles (from chloroform–methanol), m. p. 175—177°, $[\alpha]_D$ +6° (*c* 1·90) (Found : C, 80·65; H, 11·15. $C_{30}H_{48}O_2.\frac{1}{2}CH_4O$ requires C, 80·25; H, 11·05%). Treatment of this compound (365 mg.) in dry pyridine (5 ml.) with benzoyl chloride (0·365 ml.) at room temperature for 14 hr. and filtration of the product in light petroleum through alumina furnished a monobenzoate ketone identical {m. p., mixed m. p., crystal form, rotation—$[\alpha]_D$ +21° (*c* 1·93 or 2·48)—and infrared spectrum (*c* 2·0 in CS_2)} with the corresponding compound described above.

Dehydrogenation of α-Onoceradienediol.—α-Onoceradienediol (4·2 g.) was heated in a metal bath at 240—260°/0·2 mm. for 45 min. The flask was cooled, black selenium (8·4 g.) added, and the mixture heated for 23 hr. at 310—320°/1 atm. The flask and its contents were powdered in a mortar and extracted (Soxhlet) with ether. The ethereal solution was evaporated to dryness and the product chromatographed over alumina (15 g.) in light petroleum. Elution with this solvent gave crude 1 : 2 : 5 : 6-tetramethylnaphthalene (180 mg.) characterised as its picrate.

Dehydrogenation of α-Onoceradiene.—α-Onoceradiene (3·56 g.) was heated at 195°/0·2 mm. for 1 hr. Black selenium (6·2 g.) was stirred into the melt, and the mixture heated in a stream of nitrogen at 310—320° for 24 hr. Soon after the mixture had attained this temperature there was a vigorous evolution of gas. This had ceased after 24 hr. The residue was extracted as described above and the product chromatographed over alumina (100 g.) in light petroleum. Elution with this solvent (four fractions) gave 1 : 2 : 5-trimethylnaphthalene (1·91 g., 68% based on two moles from one mole of α-onocerene), characterised as the picrate (2·42 g.), m. p. 137—139° alone or mixed with an authentic specimen of m. p. 135—137°, as the styphnate, m. p. 129—131° alone or mixed with an authentic specimen of m. p. 129—131°, and as the trinitrobenzene adduct, m. p. 158—159° (Ruzicka *et al.*, *Helv. Chim. Acta*, 1930, **13**, 1411, give m. p. 159°).

Dehydrogenation of Dinoronocerane.—Freshly dried anhydrous hydrazine was distilled over in an all-glass apparatus into diethylene glycol (250 ml.; redistilled) until the solution boiled evenly at 180° (see Barton, Ives, and Thomas, *J.*, 1955, 2056). The tetra-ketone (XII) (see above) (5·0 g.) was added and the solution refluxed at 180° for 14 hr. Excess of hydrazine was distilled out until the temperature reached 210°, and the solution refluxed for 6 hr. Filtration of the product in light petroleum through alumina and crystallisation from chloroform–methanol gave *dinoronocerane* (2·3 g.), long needles, m. p. 117—119°, $[\alpha]_D$ +62° (*c* 2·47 or 2·62) (Found : C, 86·8; H, 13·0. $C_{28}H_{50}$ requires C, 86·95; H, 13·0%). When the tetraketone was reduced under standard Wolff–Kishner conditions in a sealed tube only intractable products resulted.

Dinoronocerane was not dehydrogenated by twice its weight of selenium at 310—320° for 16 hr. (70% recovery of crystalline starting material). The hydrocarbon was, however, smoothly dehydrogenated as follows. It (1·0 g.) was kept at 160—170°/0·2 mm. for 1 hr., well mixed with black selenium (2·0 g.), and then heated in a metal bath at 355—365° for 18 hr. Gas evolution, marked during the first hour, had ceased at the end of this period. The product was extracted with ether and processed as above. Elution with light petroleum and vacuum-sublimation gave 1 : 5-dimethylnaphthalene (213 mg.), identified by m. p. (79·5—80·5°) and mixed m. p. (79—80°) with an authentic specimen (m. p. 78—79·5°). The identity was

confirmed by a comparison of ultraviolet absorption spectra, $\lambda_{max.}$ 275, 286, and 297 mμ (ε 7100, 8800, and 6100), with that of the authentic specimen.

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The Hydrolysis of Amides of Dibasic Acids. Part III. The Acid Hydrolysis of Methyl-, Nitro-, and Amino-malonamides and of Methylmalonamic Acid.*

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Rates of hydrolysis in excess of hydrochloric acid of methyl-, nitro-, and amino-malonamides at 80° and 98° and of methylmalonamic acid at 80° have been measured. The results are compared with those for malonamide and malonamic acid (Part I *) and for oxamide and oxamic acid (Part II *). No simple relationship has been found between the electron-repelling or electron-attracting properties of the substituent groups and the observed rates of hydrolysis.

IN Part I * the results of an investigation of the kinetics of hydrolysis of both malonamide and malonamic acid, in large molar excess of hydrochloric acid at 80° and 98°, were given. In the present work the kinetic study has been extended, under the same conditions of acid hydrolysis, to the *C*-substituted derivatives, methyl-, nitro-, and amino-malonamides and methylmalonamic acid.

EXPERIMENTAL AND RESULTS

Methylmalonamide was prepared by the action of saturated alcoholic ammonia at 130° (in sealed tubes) on ethyl methylmalonate. After several recrystallisations from alcohol it had m. p. 208°.

Nitromalonamide was made by the nitration of malonamide, following Ruhemann and Orton's method as modified by Johnson and Nicolet (*J. Amer. Chem. Soc.*, 1914, **36**, 361). After two recrystallisations from water it melted at *ca.* 174° (decomp., varying considerably with rate of heating).

Aminomalonamide was prepared by the reduction of nitromalonamide by aluminium amalgam (Johnson and Nicolet, *loc. cit.*) and after several recrystallisations from alcohol melted at 187° (decomp.).

Methylmalonamic acid was obtained from ethyl methylmalonate as follows: (*a*) the diethyl ester was converted into ethyl hydrogen methylmalonate by controlled hydrolysis with alcoholic potassium hydroxide at room temperature; (*b*) the acid ester was converted into ammonium methylmalonamate by keeping it with excess of anhydrous liquid ammonia for two days in a sealed tube at room temperature; (*c*) after the excess of ammonia had evaporated, the salt was dissolved in alcohol and dry hydrogen chloride bubbled through until the pH was reduced to approximately 2. Precipitation of ammonium chloride was completed by addition of ether and, after filtration, the solution was evaporated to an oil which crystallised on the addition of a little ether. The methylmalonamic acid so obtained was recrystallised several times from diethyl ketone (yield, 8%, on acid ester) and had m. p. 104—106° (decomp.) (Found: N, 12·3%; acid equiv., 120. $C_4H_7O_3N$ requires N, 12·0%; acid equiv., 117·1).

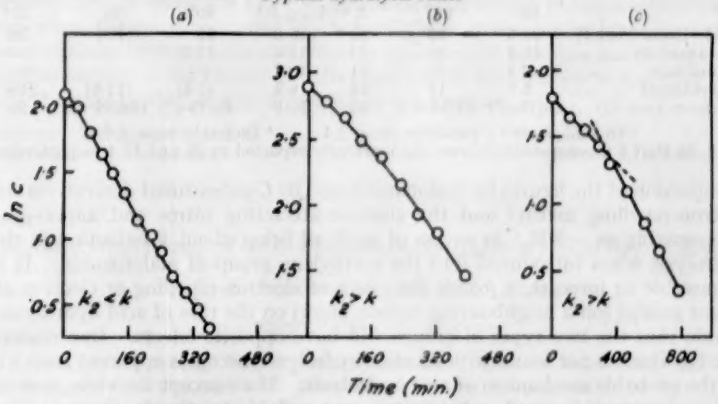
The experimental and analytical methods for the kinetic runs were essentially the same as described in Part I. Methylmalonamide, methylmalonamic acid, and nitromalonamide did not react appreciably with sodium hypobromite under the experimental conditions, so that the

* Parts I and II, *J.*, 1952, 4516, 3264.

direct method for the estimation of ammonia in the presence of unhydrolysed amide was used. However, aminomalonamide reacted with hypobromite, and the ammonia formed by hydrolysis was separated by distillation before being estimated.

Hydrolyses were followed for each compound at 80° and, except for methylmalonamic acid, at 98°, within the range [HCl] = 0·125—0·75M. In all cases runs were repeated, sometimes six times. First-order kinetics were assured, as before, by the use of a molar concentration ratio of acid : amide $\geqslant$ 100 : 1. For each run $\ln(a - x)$ was plotted against time. For each of the three diamides at any particular acid concentration the plot was linear up to about 50% hydrolysis. With methylmalonamide there was a very slight bending upwards beyond this point, corresponding to a very small falling off in the rate of hydrolysis of the second amide group (Fig., *a*) whereas with nitromalonamide there was a similarly small but opposite deviation from linearity, indicating that the second amide group in this case was hydrolysed very slightly more rapidly than the first (Fig., *b*). With aminomalonamide the second amino-group was hydrolysed sufficiently more rapidly than the first for it to be possible to draw two straight lines, one through the points corresponding to hydrolysis of less than 50% and the other through the points representing hydrolysis of greater than 50% (Fig., *c*).

Typical hydrolysis runs.



For meaning of k and k_2, see Part I (*loc. cit.*).
(*a*) Methylmalonamide in 0·25M-HCl at 80°. (*b*) Nitromalonamide in 0·625M-HCl at 80°.
(*c*) Aminomalonamide in 0·375M-HCl at 80°.

From the linear parts of these graphs corresponding to the first half of the hydrolysis, the values of the pseudo-unimolecular rate constants, k, measuring the rate of hydrolysis of the first amide group, were determined. The values so obtained were independent of the initial concentration of the amide, confirming the pseudo-unimolecularity of the hydrolysis under the conditions used. The rates of hydrolysis of the second amide group in aminomalonamide (*i.e.*, of the amide group in aminomalonamic acid) have been calculated from the slopes of the linear plots of the second half of the hydrolysis. The values of k_2 so obtained are probably less accurate than those of k (first amide group). The results for all three diamides are summarised in Table 1, the mean values

TABLE 1. *Pseudo-unimolecular rate constants* $\times 10^3 (min.^{-1})$.

		[HCl], M						
	Temp.	0·125	0·25	0·375	0·50	0·625	0·75	k/[HCl]
Methylmalonamide (k)	80°	2·9	5·1	—	10·6	—	16·0	21·3
,, ...	98	11·5	21·3	33·0	45·0	—	—	90·0
Methylmalonamic acid (k_2)	80	2·7	5·1	6·8	8·6	—	13·7	17·5 ± 1
Nitromalonamide (k)	80	—	1·4	2·3	2·9	3·8	4·6	6·4
,, ...	98	—	6·5	10·0	13·6	16·7	20·1	27·0
Aminomalonamide :								
1st amide group (k)	80	—	—	1·2	2·0	2·1	2·6	3·7
,, ...	98	1·4	2·7	4·9	6·7	—	10·3	13·0
2nd amide group (k_2).....	80	—	—	2·4	2·8	3·3	4·2	5·2
,, ...	98	2·1	4·0	7·0	9·0	—	15·0	17·6

only of k (or k_2) being given for each substance at each particular acid concentration. The agreement between the values obtained from repeated runs was in general of the same order as in the earlier work (Part I) and, for brevity and clarity, individual values have therefore been omitted.

To test the conclusions drawn from the slight curvatures of the $\ln(a - x)$–time plots (Fig., *a* and *b*), methylmalonamic acid was prepared and used in hydrolyses at 80° (but not at 98°). The $\ln(a - x)$–time plots were now linear throughout each run, and the values of k_2 calculated therefrom (Table 1) afford direct confirmation that the second amide group in methylmalonamide is, in fact, hydrolysed at a slightly, but measurably, smaller rate than the first amide group ($k_2 < k$, Fig., *a*).

Discussion

Table 2 brings together the results given in this and in Parts I and II for acid-catalysed hydrolysis of diamides.

Table 2. *Catalytic coefficients, $k_{H^+} \times 10^3$, and Arrhenius parameters.*

	First amide group				Second amide group			
	80°	98°	E [a]	$\log_{10} B$ [b]	80°	98°	E [a]	$\log_{10} B$ [b]
Malonamide (from Part I)	23·6 [c]	93	20 [c]	10·8	32	100	16	8·7
Methylmalonamide	21·3	90	21	11·4	17·5	—	—	—
Nitromalonamide	6·4	27	21	10·7	—	—	—	—
Aminomalonamide	3·7	13	18	8·9	(5·2)	(17·6)	(18)	(8·8)
Oxamide (from Part II) ...	25(79·5°)	97(97·5°)	20	10·8	48(79·5°)	184(97·5°)	20	11·0

[a] In kcal. mole^{-1}; probable error ±1 [b] Probable error ±0·5.
[c] In Part I these quantities were inadvertently reported as 26 and 18·4 respectively.

A comparison of the figures for malonamide and its *C*-substituted derivatives shows that the electron-repelling methyl and the electron-attracting nitro- and amino-groups (the latter presumably as $-NH_3^+$ in excess of acid) all bring about a reduction in the rate of acid hydrolysis when introduced into the methylene group of malonamide. It is clearly not yet possible to forecast, *a priori*, the effect of electron-repelling or electron-attracting substituent groups (on a neighbouring carbon atom) on the rate of acid hydrolysis, or even to conclude that the two types of groups will have opposite effects. One reason for this uncertainty, which is not found with alkaline hydrolysis, becomes apparent from a consideration of the probable mechanism of acid hydrolysis. If we accept the view, now supported by much indirect evidence (Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953; Bunton, Lewis, and Llewellyn, *Chem. and Ind.*, 1954, 1154), that in acid hydrolysis the protonated form of the amide is the entity which is attacked by the nucleophilic water and that the equilibrium between the protonated and the unprotonated form is rapidly established, two opposing polar effects of a substituent group are recognisable. The first concerns the equilibrium concentration of the protonated form, which should be favoured by electron-repelling groups and *vice versa*; the second effect concerns the ease of attack at the carbonyl-carbon atom of the protonated amide by the nucleophilic water molecule and here electron-attracting groups should facilitate the process and electron-repelling groups hinder it. Until it is possible to deduce which of these two polar effects predominates for any particular group and situation, the electronic effect of the substituent group on the rate of acid hydrolysis cannot be predicted.

$$R{\cdot}CH_2{\cdot}CO{\cdot}NH_3 + H_3O^+ \overset{\text{rapid}}{\rightleftharpoons} R{\cdot}CH_2{\cdot}C(OH){\cdot}NH_3 + H_2O$$

$$H_2O: + \begin{matrix} CH_2R \\ CO{\cdot}\overset{+}{N}H_3 \end{matrix} \longrightarrow \left[\begin{matrix} \overset{\delta+}{H_2O} \cdots \\ \end{matrix} \begin{matrix} CH_2R \\ CO \\ \end{matrix} \cdots \overset{\delta+}{NH_3} \right] \longrightarrow H_2O^+{-}\begin{matrix} CH_2R \\ CO \end{matrix} + :NH_3 \quad (A_{Ac}2)$$

$$R{\cdot}CH_2{\cdot}CO_2H_2^+ + NH_3 \xrightarrow{\text{rapid}} R{\cdot}CH_2{\cdot}CO_2H + NH_4^+$$

Arguments have been given for the view that, where the $A_{Ac}2$ mechanism is operative, polar effects are weak and are liable to be masked by stronger steric effects (Ingold, *op. cit.*). Our results can be regarded as consistent with such a general conclusion. However it is only in aminomalonamide that the substituent group produces a significant change in either

the Arrhenius energy of activation or the entropy ($\log_{10} B$) term. It is difficult to understand why such an effect should show up in this way for the amino- but not for the nitro- and methyl groups, unless it be assumed that there is an indirect entropy effect resulting from the positive ionic charge on the $-NH_3^+$ group (which is presumed to be present, to the virtual exclusion of the NH_2 group, in the large molar excess of acid used). Such an effect might result if the positive ammonium-ion group could, by coulombic interaction with the strongly polar protonated amide group, effectively control the conformation of the latter group with respect to the rest of the molecule.

The three substituent groups, methyl-, nitro-, and amino-, all bring about a reduction in the rate of acid hydrolysis of the amide group of malonamic acid when introduced at the methylene carbon atom. The amic acids (including oxamic acid) all fall into the same order for the relative rates of acid hydrolysis as do the diamides. A comparison of the corresponding amic acid and diamide shows that the replacement of an amide group by a carboxyl group increases the rate at which the remaining amide group undergoes acid hydrolysis, except for methylmalonamide where the opposite effect is observed. As would be expected, the accelerating effect of a carboxyl as compared with an amide group is considerably greater when the two groups are directly linked to one another (in oxamic acid) than when they are separated by a methylene group (in malonamic acid). The replacement of an amide by a carboxyl group in malonamide produces much bigger changes (partly compensating) in the energy of activation and in the entropy factor than it does in oxamide. The explanation of this difference is not obvious.

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Raman Spectrum of the Tetrabromogallate(III) ($GaBr_4^-$) *Ion.*

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An approximately 1·5M-aqueous solution of gallium tribromide containing 6M-hydrobromic acid gives four Raman frequencies: 71 cm.$^{-1}$, strong, sharp, depolarized; 102 cm.$^{-1}$, strong, sharp, depolarized; 210 cm.$^{-1}$, very strong, sharp, polarized; and 278 cm.$^{-1}$, rather weak, diffuse, depolarized. This spectrum is attributed to the ion $GaBr_4^-$, of regular tetrahedral shape.

CONTINUING previous work, in which the Raman spectrum of the $InBr_4^-$ ion was observed (Woodward and Bill, *J.*, 1955, 1699), we have observed a spectrum attributable to the corresponding ion $GaBr_4^-$. The aqueous solution contained both gallium tribromide (*ca.* 1·5M) and hydrobromic acid (6M). The observed Raman frequencies, estimated intensities, appearances of lines, states of polarization, and assignments are given in Table 1.

Table 1. *Raman spectrum of the* $GaBr_4^-$ *ion.*

$\Delta\nu$ (cm.$^{-1}$)	71	102	210	278
Intensity	strong	strong	very strong	rather weak
Appearance	sharp	sharp	sharp	diffuse
Polarization	depolarized	depolarized	strongly polarized	depolarized
Assignment	ν_2 (E)	ν_4 (F_2)	ν_1 (A_1)	ν_3 (F_2)

The number of observed frequencies and the states of polarization provide strong evidence of a species XY_4 of regular tetrahedral shape, and the spectrum may be confidently attributed to the ion $GaBr_4^-$. This must be the predominant species in the solution investigated.

Table 2 gives a comparison of the frequencies of the ions $GaBr_4^-$, $InBr_4^-$ (Woodward and Bill, *loc. cit.*), and $TlBr_4^-$ (Delwaulle, *Compt. rend.*, 1954, **238**, 2522). It is seen that each of the frequencies shows a gradual decrease in the order: gallium, indium, thallium.

As far as the totally symmetrical " breathing " frequencies ν_1 are concerned, this indicates that the stretching force constant k of the metal–bromine bond decreases in the order given. The values of $10^{-5}k$ calculated on the basis of a simple valency force field are: $GaBr_4^-$, 2·08; $InBr_4^-$, 1·83; and $TlBr_4^-$, 1·70 dynes per cm.

TABLE 2. *Vibrational frequencies of complex ions* MBr_4^- *of Group* IIIB *elements.*

	ν_2	ν_4	ν_1	ν_3
$GaBr_4^-$	71	102	210	278
$InBr_4^-$	55	79	197	239
$TlBr_4^-$	51	64	190	209

The $GaBr_4^-$ ion is isoelectronic with the neutral germanium tetrabromide molecule. The observed Raman frequencies are compared in Table 3, where the values for germanium tetrabromide are those given by Herzberg (" Molecular Spectra and Molecular Structure," van Nostrand Co., New York, 1945, Vol. 2, p. 167). A corresponding comparison for the related isoelectronic pair, stannic bromide (Herzberg, *op. cit.*) and $InBr_4^-$ (Woodward and Bill, *loc. cit.*), is also given.

TABLE 3. *Vibrational frequencies of isoelectronic species.*

	ν_2	ν_4	ν_1	ν_3		ν_2	ν_4	ν_1	ν_3
$GeBr_4$	78	111	234	328	$SnBr_4$	64	88	220	279
$GaBr_4^-$	71	102	210	278	$InBr_4^-$	55	79	197	239
$\nu_{GeBr_4}/\nu_{GaBr_4^-}$	1·10	1·09	1·11	1·18	$\nu_{SnBr_4}/\nu_{InBr_4^-}$ ...	1·16	1·11	1·12	1·17

From Table 3 it is seen that the frequencies attributed to $GaBr_4^-$ in the present work bear to the frequencies of the isoelectronic germanium tetrabromide molecule a relationship which is very similar to that borne by the frequencies of $InBr_4^-$ to the isoelectronic stannic bromide.

The spectrum of $GaBr_4^-$, like that of $TlBr_4^-$ as reported by Delwaulle (*loc. cit.*), is shown by an aqueous solution of the tribromide in presence of hydrobromic acid, but corresponding aqueous solutions of indium tribromide in presence of hydrobromic acid (up to 6M) do not show the spectrum of $InBr_4^-$. The latter spectrum is only observed for extracts from the aqueous phase into organic solvents. Thus, although indium occupies a position in Group IIIB intermediate between gallium and thallium, the tendency to form the ion MBr_4^- in aqueous solution is less for indium than for either gallium or thallium.

These investigations are being extended.

EXPERIMENTAL

A known weight of pure gallium, supplied by Messrs. Johnson, Matthey and Co., was dissolved in the appropriate amount of bromine-free hydrobromic acid (approx. 11M) to give a nearly 1·5M-solution of gallium tribromide containing 6M excess of acid.

The Raman spectra were photographed with " Toronto arc " excitation with the apparatus previously described (George, Rolfe, and Woodward, *Trans. Faraday Soc.*, 1953, **49**, 375), slightly modified to allow of the insertion of Polaroid cylinders around the Raman tube. The states of polarization of the Raman lines were investigated by Rank and Kagarise's method (*J. Opt. Soc. Amer.*, 1950, **40**, 89), successive spectra being photographed with cylinders having their directions of polarization respectively parallel and perpendicular to the tube axis. Frequencies were determined in the usual way with an interpolation formula based upon a copper-arc spectrum as standard. The estimated limits of error in the measured values of $\Delta\nu$ are $\pm$ 2 cm.$^{-1}$. The principal exciting line was that of mercury at 4358 Å. A sodium nitrite filter was used to diminish the intensity of primary lines of lower wavelength. The Raman spectrum of $GaBr_4^-$ could be observed clearly with an exposure time of 1 hr. without Polaroid cylinders.

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αβ-*Unsaturated Aldehydes and Related Compounds. Part VII.* Thermal Fission of* 1 : 1 : 3-*Trialkoxypropanes.*†

By R. H. Hall and E. S. Stern.

[Reprint Order No. 6308.]

Catalysed pyrolysis of 1 : 1 : 3-trialkoxypropanes in the liquid or the vapour phase gave mixtures of the acraldehyde dialkyl acetals and *cis*- and *trans*-1 : 3-dialkoxypropenes. 1 : 1 : 3-Triacetoxypropane behaved analogously, yielding acraldehyde diacetate (allylidene diacetate) and 1 : 3-diacetoxypropene.

For a series of 1 : 1 : 3-trialkoxypropanes the relative proportions of the products depended on the nature of the alkoxy-groups, and formation of the acetals was favoured by more drastic conditions, partly because the 1 : 3-dialkoxypropenes then isomerised.

Both fission products added alcohols in presence of acidic catalysts and regenerated the 1 : 1 : 3-trialkoxypropanes, the 1 : 3-dialkoxypropenes apparently doing so the more readily.

Hydrogenation of the 1 : 3-dialkoxypropenes and of 1 : 3-diacetoxypropene afforded trimethylene glycol diethers and diacetate, respectively.

The work reported here arose out of the desire to prepare simple acetals of acraldehyde (cf. Part V; *J.*, 1954, 3388). Since the usual laboratory methods, namely, reaction of acraldehyde with orthoformic esters (Fischer and Baer, *Helv. Chim. Acta*, 1935, **18**, 514; Schmidt, G.P. 553,177) or dehydrochlorination of 1 : 1-dialkoxy-3-chloropropanes (cf. Witzemann, Evans, Hass, and Schroeder, *Org. Synth.*, 1931, **11**, 1), were not entirely suitable for large-scale application, and since direct formation of the acetals from the aldehyde and alcohols proved unsatisfactory (cf. Part V), other methods were examined. The present paper describes the catalysed thermal fission of 1 : 1 : 3-trialkoxypropanes which yielded both the acetals and the isomeric 1 : 3-dialkoxypropenes. Since this work was completed (in 1950), Whetstone and Shell Development Co. (U.S.P. 2,626,283) and Myers, Magerlein, Staffen, and the Upjohn Co. (B.P. 713,088) have reported the direct conversion of acraldehyde into its lower dialkyl acetals, a porous calcined silica–alumina hydrogel being used as catalyst by the former authors, and sharply-defined trace amounts of certain specified acids by the latter.

The trialkoxy-compounds required as starting materials in the present investigation were accessible by direct acid-catalysed condensation of alcohols with acraldehyde, but the yields obtainable in this reaction, which has long been known (cf. Alsberg, *Jahresber.*, 1864, 495), were not always satisfactory (cf. Schulz and Wagner, *Angew. Chem.*, 1950, **62**, 105). However, removal of the water produced in the reaction by azeotropic distillation with an inert entrainer (Bellringer, Bewley, Hall, Jacobs, and Stern, *J. Appl. Chem.*, 1954, **4**, 679; cf. B.P. 713,833; B.P. Appln. 9158/52) gave very high yields (better than 90% in some cases) and the trialkoxy-compounds thus became readily available.

Trialkoxypropanes in which the alkoxy-groups were dissimilar, such as 3-butoxy-1 : 1-diethoxy- and 1 : 1-dibutoxy-3-ethoxy-propane, were not obtainable by the entrainment method and were prepared under mild conditions from the appropriate β-alkoxypropaldehyde and alcohol in the presence of an acid catalyst. The absence of any cross-etherification during the acetal formation was proved by mild acid hydrolysis of the trialkoxy-compound and characterisation of the derived β-alkoxypropaldehyde; in each case a homogeneous derivative of the original alkoxy-aldehyde was obtained.

The thermal fission of polyalkoxy-compounds is not new: acetals have been cracked to vinyl ethers with the loss of one molecule of alcohol in the liquid phase (Claisen, *Ber.*, 1898, **31**, 1006, 1019), in the vapour phase over a variety of solid catalysts (Sigmund *et al.*, *Monatsh.*, 1929, **51**, 234; 1927, **48**, 267; 1928, **49**, 271; Johanissian and Akunian, *Chem. Zentr.*, 1930, II, 552; Cabanac, *Compt. rend.*, 1930, **190**, 881; I.G. Farbenind., G.P. 525,836;

* Part VI, *J.*, 1954, 4303. † Part of this work is described in B.P. 695,789 and 709,913.

B.P. 345,253; Consortium für Electrochem. Ind., G.P. 560,354) and also in the vapour phase in presence of gaseous catalysts (Bramwyche, Mugdan, and the Distillers Co. Ltd., B.P. 603,471). Moreover, 1 : 1 : 3-trialkoxybutanes, the homologues of the compounds now studied, have been decomposed in the vapour and the liquid phase over solid catalysts, with the loss of two molecules of alcohol, to 1-alkoxybuta-1 : 3-dienes (Flaig, *Reichsamt f. Wirtschaftsausbau, Chem. Ber.*, 1942, 1073, abstracted in *Chem. Abs.*, 1947, **41**, 6190; see also *Annalen*, 1950, **568**, 1; Meier, *Ber.*, 1944, **77**, 108; Marion and Farmilo, *Canad. J. Res.*, 1947, **25**, *B*, 118; Farmilo and Nicholls, *ibid.*, 1950, **28**, *B*, 689); only traces of 1 : 3-dialkoxybut-1-enes are obtained in this reaction (Flaig, *locc. cit.*). Analogously, 1 : 3 : 3-trialkoxybutanes in the liquid phase over potassium hydrogen sulphate give 2-alkoxybuta-1 : 3-dienes (Dykstra, *J. Amer. Chem. Soc.*, 1935, **57**, 2255), whilst over alumina the corresponding 1 : 3-dialkoxybut-2-ene is obtained in good yield.

A preliminary investigation of the homogeneous gas-phase decomposition of the 1 : 1 : 3-trialkoxypropanes under conditions similar to those of Bramwyche and Mugdan (*loc. cit.*) revealed that these compounds readily lost one molecule of alcohol, giving a mixture of the two theoretically possible structural isomers, the 1 : 3-dialkoxypropene (*A*) and the acraldehyde dialkyl acetal (*B*), which were separable by fractional distillation.

$$(B)\ CH_2{:}CH{\cdot}CH(OR)_2 \longleftarrow RO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OR)_2 \longrightarrow RO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}OR\ \ (A)$$

The structures were readily established by mild hydrolysis with very dilute aqueous acid, the lower-boiling acetals giving acraldehyde, whilst the 1 : 3-dialkoxypropenes afforded the β-alkoxypropaldehydes, characterised as 2 : 4-dinitrophenylhydrazones. Further, the diethyl acetal was compared with that prepared by the unequivocal method of Fischer and Baer (*Helv. Chim. Acta*, 1935, **18**, 514), and the hydrogenation product of 1 : 3-dimethoxypropene with synthetic 1 : 3-dimethoxypropane (Baker and Field, *J.*, 1932, 86).

Each of the 1 : 3-dialkoxypropenes, a new class of compound, can exist in two geometrically isomeric forms, and *cis*- and *trans*-1 : 3-dichloropropenes are, in fact, well known (cf. Hatch and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 1196; Hatch, Gordon, and Russ, *ibid.*, 1948, **70**, 1093). In the present work, it was possible to separate partly *cis*- and *trans*-1 : 3-diethoxypropene by careful fractional distillation of the cracking product. The isomers, and, in particular, the *trans*-compound, were, however, not very stable to the prolonged heat treatment involved in a lengthy fractional distillation, and, although pure *cis*-isomer was obtained, the best sample of the higher-boiling *trans*-isomer isolated still contained about 25% of the *cis*-compound. The isomers were differentiated by infrared spectroscopy; the *cis*-isomer gave a characteristic broad peak at 746 cm.$^{-1}$, and the *trans*-isomer a sharp maximum at 939 cm.$^{-1}$ [cf. *cis*- and *trans*-but-1-enyl butyl ether (Hall, Philpotts, Stern, and Thain, *J.*, 1951, 3341)]. Both isomers showed a striking absorption band in the region 1660—1665 cm.$^{-1}$ by which they could readily be differentiated from the acraldehyde acetals whose spectra lacked a band in this region although they all had a characteristic maximum at 938 cm.$^{-1}$ (cf. Part V). The infrared spectra of all the 1 : 3-dialkoxypropenes prepared were remarkably similar and resembled that of a mixture of *cis*- and *trans*-1 : 3-diethoxypropene, so that it may be assumed that an equilibrium mixture of the isomers was generally produced in the thermal fission.

The 1 : 3-dialkoxypropenes had a pleasant odour, very different from that of the acraldehyde acetals, and were slightly water-soluble (about 5% v/v in the case of 1 : 3-diethoxypropene). As αβ-unsaturated ethers they very readily added alcohols in presence of acidic catalysts and regenerated 1 : 1 : 3-trialkoxypropanes; on hydrogenation over Raney nickel in neutral (ethanolic) solution they gave almost quantitatively the 1 : 3-dialkoxypropanes. 1 : 3-Dimethoxy- and 1 : 3-diethoxy-propane have previously been prepared in very poor yield by alkylation of propane-1 : 3-diol or its monoethers (Noyes, *Amer. Chem. J.*, 1897, **19**, 768; Baker and Field, *loc. cit.*) or by the reaction of 3-chloropropanol with sodium alkoxide (Rojahn and Lemme, *Arch. Pharm.*, 1925, **263**, 617); they may also be obtained by high-pressure hydrogenation of 1 : 1 : 3-trialkoxypropanes in alcohol over Raney nickel at 195° (Schulz and Wagner, *Angew. Chem.*, 1950, **62**, 105; see also FD 2464/49, G.P. Appl. D 78,864 IVd/12o; PB 70,309, Frame 7649; and PB 73,333,

Frames 4297 and 4521), but this method is not attractive because of the vigorous conditions required and because the great reactivity of Raney nickel towards the solvent under these conditions introduces explosion hazards (personal communication from Mr. I. K. M. Robson).

Of the acraldehyde dialkyl acetals obtained in this investigation, the dimethyl and diethyl compounds were well known (cf., *e.g.*, Wohl and Momber, *Ber.*, 1914, **47**, 3348) and the di-*n*-propyl and di-*n*-butyl homologues had been isolated previously (cf. Part V). The di*iso*propyl acetal, however, was not accessible by the earlier methods, and was obtained for the first time; an alternative method of preparation was subsequently recorded by Myers, Magerlein, Staffen, and the Upjohn Chemical Co. (*loc. cit.*).

One notable feature of the fission described here was that both products, the acraldehyde acetal and the 1 : 3-dialkoxypropene, could be reconverted almost quantitatively into 1 : 1 : 3-trialkoxypropane simply by treatment with the appropriate alcohol in the cold in the presence of an acidic catalyst: the process was thus capable of adaptation to the preparation of either of the reaction products, the unwanted product being converted into starting material and recycled with no significant loss of material.

Owing to this ready addition of alcohol to both the unsaturated acetal and the ether, it was necessary to neutralise the acid catalyst in the fission products before they were cooled, either by adding a base to the hot gaseous mixture, or by feeding a tertiary heterocyclic base with the starting materials (cf. Bramwyche and Mugdan, *loc. cit.*): the latter procedure was adopted, quinoline being employed in place of the pyridine advocated by Bramwyche and Mugdan (*loc. cit.*) as the latter was too low-boiling for the present experiments and in some cases, after distillation of the reaction products, contaminated the desired fractions.

The effects of changes of reaction conditions (particularly contact time, temperature, and catalyst concentration) were studied briefly with 1 : 1 : 3-triethoxypropane. Variation of the contact time at 350° or of the reaction temperature between 250° and 450° (Table 1)

TABLE 1. *Effect of variation of contact time and temperature on thermal fission of* 1 : 1 : 3-*triethoxypropane.*

Catalyst: di*iso*propyl sulphate (0·1 mole-%) in presence of quinoline (3·0 mole-%).

Temp.	Contact time (sec. at operating temp.)	Unchanged material recovered (%)	Yield of products (%), based on starting material consumed		
			EtOH	$CH_2{:}CH{\cdot}CH(OEt)_2$	$EtO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}OEt$
350° ± 5°	28	25	97	47·5	40
,,	56	17	94	44	42
,,	98	17	93	42	42
265	160	58	100	36·5	47
350	56	17	94	44	42
ca. 450	*ca.* 4·3	32	102	28·5	51·5

TABLE 2. *Behaviour of reaction products under conditions for thermal fission.*

In each run 0·1 mole-% of di*iso*propyl sulphate and 1 mole-% of a base were added.

Substance	Base	Temp.	Contact time (sec. at operating temp.)	Unchanged material recovered (%)	Yield of products (%), based on starting material consumed		
					EtOH	$CH_2{:}CH{\cdot}CH(OEt)_2$	$EtO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}OEt$
Acraldehyde diethyl acetal	Pyridine	360°	65	90	—	85—90% recovery	—
1 : 3-Diethoxypropene	Quinoline	350	53	58	Not detd.	37	58—60% recovery

gave rather inconclusive results but it appeared that the production of 1 : 3-diethoxypropene was favoured, at the expense of the acetal, when the conversion of 1 : 1 : 3-triethoxypropane was reduced (*i.e.*, when the recovery of unchanged starting material was increased), irrespective of furnace temperature. This effect was ascribed to the relatively high thermal instability of 1 : 3-diethoxypropene; thus it was found (Table 2) that, under

similar conditions at 350°, acraldehyde acetal passed through the reaction tube substantially unchanged; 1 : 3-diethoxypropene was partly split and isomerised, giving ethanol and acraldehyde diethyl acetal—the probability that one of the geometrical isomers was less stable than the other was not investigated experimentally. The partial isomerisation of 1 : 3-diethoxypropene to the acetal was surprising, in view of the reverse isomerisation under acid conditions of 3 : 3-diacetoxy- (cf. Smith, Norton, and Shell Development Co., B.P. 638,763; Smith, Norton, and Ballard, *J. Amer. Chem. Soc.*, 1951, **73**, 5282), 3 : 3-dichloro-, and 3 : 3-dibromo-prop-1-ene (cf. Romburgh, *Bull. Soc. chim. France*, 1881, **36**, 550; 1882, **37**, 103; Stitz, *Oesterr. chem. Ztg.*, 1947, **48**, 186).

Further evidence of the lower stability, under the conditions of the reaction, of 1 : 3-diethoxypropene compared with the acetal was obtained from varying the concentration and proportion of catalyst (see Table 3): the relative amount of 1 : 3-diethoxypropene formed was greatest under mild reaction conditions, when the product presumably underwent little further change. Thus catalyst concentrations of 0·06 and 0·1 mole-% (at a catalyst to neutraliser molar ratio of 1 : 10) gave about twice as much acraldehyde acetal as 1 : 3-diethoxypropene, but with 0·2 mole-% catalyst this proportion rose to 12. An increase in the amount of quinoline (used as neutralising base) greatly increased the amount of 1 : 3-diethoxypropene isolated, and the base may thus have acted as stabiliser for the diether as well as subsequently fulfilling its role of neutralising the catalyst and preventing recombination of the unsaturated ether with alcohol. Moreover, an increase in the amount of neutraliser used (from a 10- to a 30-fold excess) reduced the amount of starting material recovered, and it therefore seemed possible that the smaller excess was insufficient for the complete prevention of addition of ethanol to the enolic ether; this addition thus appeared to proceed much more readily than that of ethanol to acraldehyde acetal. A catalyst to neutraliser molar ratio of 1 : 30 was therefore desirable to ensure a reproducible, good yield of 1 : 3-diethoxypropene, but a greater excess of neutraliser conferred no further advantage.

TABLE 3. *Effect of variation in catalyst concentration and in catalyst to neutraliser ratio* (temp. 350°).

$Pr^i_2SO_4$ concn. (mole-%)	Quinoline concn. (mole-%)	Ratio, catalyst : neutraliser	Contact time (sec.)	Unchanged material recovered (%)	Yield of products (%), based on starting material consumed		
					EtOH	$CH_2{:}CH{\cdot}CH(OEt)_2$	$EtO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}OEt$
0·1	0	—	90	18	98	50	15
0	3	—	53	83	15 *	5 *	37 *
0·06	0·6	1 : 10	54	26	100	49·5	25
0·1	1·0	1 : 10	57	33	90	58	24
0·2	2·0	1 : 10	42	29	97	65	6
0·1	3·0	1 : 30	56	17	94	44	42
0·1	6·0	1 : 60	45	16	94	48	40

* Low recoveries of products are probably due to a combination of distillation losses and very low conversion (<17%).

TABLE 4. *Thermal fission of* 1 : 1 : 3-*triethoxypropane.*

Catalyst and concn. (mole-%)		Neutraliser and concn. (mole-%)		Temp.	Contact time (sec.)	Unchanged material recovered (%)	Yield of products (%), based on consumed starting material		
							EtOH	$CH_2{:}CH{\cdot}CH(OEt)_2$	$EtO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}OEt$
Me_2SO_4	1	Pyridine	3	370°	85	18	104	35	17
H_2SO_4	0·5	—*	—	360	84	10	107	37	5
—	—	—	—	360	64	>90	—	—	—
—	—	Quinoline	3	355	53	83	15	5	37

* Quinoline (3 mole-%) in receiver to neutralise catalyst.

Use of quinoline alone (in absence of acidic catalyst) resulted in little decomposition (cf. Table 4): the useful cracking product, however, contained much more 1 : 3-diethoxypropene than acraldehyde diethyl acetal.

For the study of the effects of changes in starting material on the relative proportions

and yields of the products, conditions were chosen under which reproducible results were obtained in the decomposition of 1 : 1 : 3-triethoxypropane (see Table 5). Similar conversions were attained for the five trialkoxypropanes examined, but it was found that trimethoxy- and tri*iso*propoxy-propane on fission gave the 1 : 3-dialkoxypropene preferentially, whilst triethoxy-, tri-*n*-propoxy-, and tri-*n*-butoxy-propane gave about equal amounts of the two structural isomers. There is no obvious explanation for these differences.

TABLE 5. *Effect of variation of starting material* [di*iso*propyl sulphate (0·1 mole-%); quinoline (3·0 mole-%); temp., 350°].

Starting material	Contact time (sec.)	Unchanged material recovered (%)	Yield of products (%), based on starting material consumed		
			ROH	$CH_2{:}CH{\cdot}CH(OR)_2$	$RO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}OR$
1 : 1 : 3-Trimethoxypropane ...	48	20	90	38	56
1 : 1 : 3-Triethoxypropane	56	17	94	44	42
1 : 1 : 3-Tri-*n*-propoxypropane...	52	18·5	83	43	45
1 : 1 : 3-Tri*iso*propoxypropane *	52·5	8·5	100	33	56
1 : 1 : 3-Tri-*n*-butoxypropane ...	49	16	98	40	41·5
1 : 1 : 3-Triethoxy-2-methylpropane	51	12·5	90	48·5	34
1 : 1 : 3-Triethoxybutane	50	0		Extensive decomp.	
1 : 1 : 3-Triacetoxypropane † ...	55	38	88	42	14

* Quinoline concn. : 2 mole-%. † Quinoline concn. : 1 mole-%.

For comparison, 1 : 1 : 3-triethoxy-2-methylpropane (from α-methylacraldehyde) and 1 : 1 : 3-triethoxybutane (from crotonaldehyde) were also submitted to the "standard" reaction conditions. Triethoxy-2-methylpropane behaved normally, except that it gave the acetal of α-methylacraldehyde preferentially (48·5% yield) and less 1 : 3-diethoxy-2-methylpropene (34%), but 1 : 1 : 3-triethoxybutane decomposed extensively and gave much 1-ethoxybuta-1 : 3-diene (also obtained by Flaig, *Chem. Abs.*, 1947, **41**, 6190; *Annalen*, 1950, **568**, 1; Meier, *Ber.*, 1944, **77**, 108) and little, if any, of the desired fission products. Much milder conditions appeared to be necessary, therefore, for the successful preparation of 1 : 3-diethoxybut-1-ene or of crotonaldehyde diethyl acetal from 1 : 1 : 3-triethoxybutane, but these were not investigated.

With two "unsymmetrical" trialkoxypropanes, 3-butoxy-1 : 1-diethoxy- and 3 : 3-dibutoxy-1-ethoxy-propane, the lower alcohol tended to be split out preferentially (see Table 6).

TABLE 6. *Thermal fission of "unsymmetrical" 1 : 1 : 3-trialkoxypropanes* (0·1 mole-% of di*iso*propyl sulphate; temp., 350°).

Starting material	Quinoline concn. (mole-%)	Contact time (sec.)	Starting material recovered (%)	Yield of products (%), based on starting material consumed			
				EtOH	BuOH	Acetal	1 : 3-Dialkoxy-cmpd.
1 : 1-Dibutoxy-3-ethoxypropane	3	50	24%	51	48	45	38
3-Butoxy-1 : 1-diethoxypropane	1	71	14%	80	13	7	71

1 : 1 : 3-Triacetoxypropane, which was less accessible than the ethers and had to be prepared by the method of Smith and Shell Development Co. (U.S.P. 2,471,391; cf. Smith, Norton, and Ballard, *loc. cit.*), was also cracked under similar conditions (except that the catalyst to neutraliser ratio was 1 : 10) (see Table 5). The product contained more unchanged starting material than that from triethoxypropane, and three times as much acraldehyde diacetate was obtained as 1 : 3-diacetoxypropene.

In order to demonstrate the wide variety of conditions suitable for the acid-catalysed fission of 1 : 1 : 3-trialkoxypropanes, experiments were carried out with different catalysts: thus sulphuric acid (vapour phase and liquid phase), methyl sulphate (vapour phase), ammonium sulphate (liquid phase), and fuller's earth (heterogeneous solid–liquid phases)

induced decomposition of triethoxypropane under the drastic reaction conditions used, giving in each case both the acetal and 1 : 3-diethoxypropene.

In conclusion, two microfilmed reports [FD 16/48 (Frames 3—4) and PB 73,507 (Frames 5066—5073)] of German war-time work (by Brendlein), which became available during this investigation, must be mentioned. These stated that pyrolysis of gaseous 1 : 1 : 3-trimethoxy- or 1 : 1 : 3-triethoxy-propane over alumina and other solid catalysts at 250—350° gave, besides alcohol, acraldehyde, and unchanged starting material, compounds designated as 1 : 3-dialkoxypropenes. Comparison of the physical constants recorded with data obtained in the present work (see Table 7), together with their reported

TABLE 7.

	German report		Present work			
			1 : 3-Dialkoxypropene		Acetal	
Alkyl	B. p.	n_D^{20}	B. p.	n_D^{20}	B. p.	n_D^{20}
Me	87—88°	1·3961	63·5°/98 mm.	1·4200	87·5—88°/750 mm.	1·3962
Et	123—124°	1·4020	82°/60 mm.	1·4238	57°/76 mm.	1·4012

ready hydrolysis to acraldehyde and alcohol, indicated, however, that they were really acraldehyde dialkyl acetals and that authentic 1 : 3-dialkoxypropenes had either not been obtained or not isolated. Repetition (by Mr. I. K. M. Robson) of the German work with trimethoxypropane gave, as expected, some acraldehyde and much methanol, together with a poor yield of acraldehyde dimethyl acetal; a little (1·5% w/w) of the higher-boiling 1 : 3-dimethoxypropene was, however, also isolated; in Brendlein's experiments this must have been present, if at all, in the distillation residues (*i.e.*, with the unchanged trimethoxypropane).

EXPERIMENTAL

Di*iso*propyl sulphate was prepared essentially by the method of Dorris and Sowa (*J. Amer. Chem. Soc.*, 1938, **60**, 358; cf. Crittenden, U.S.P. 2,504,807). Gaseous propylene was passed into concentrated sulphuric acid (98 g.) at −5° (or, initially at as low a temperature as could be attained without inducing solidification); when 80 g. had been absorbed the liquid was poured into ice-water and immediately extracted with ether. The extracts were washed with sodium carbonate solution until no acid remained, dried, and fractionated. The pure di*iso*propyl sulphate (91·5 g.) had b. p. 50°/0·2 mm., n_D^{20} 1·4080 (Dorris and Sowa, *loc. cit.*, give b. p. 98°/2 mm.).

Starting Materials.—1 : 1 : 3-Trimethoxypropane was kindly supplied by Mr. I. K. M. Robson; after fractional distillation the pure material had b. p. 94—95°/142 mm., n_D^{20} 1·4003.

1 : 1 : 3-Triethoxy-, 1 : 1 : 3-tripropoxy-, 1 : 1 : 3-tri*iso*propoxy-, and 1 : 1 : 3-tributoxy-propane, and 1 : 1 : 3-triethoxy-2-methylpropane were prepared essentially by the method of Bellringer, Bewley, Hall, Jacobs, and Stern (*J. Appl. Chem.*, 1954, **4**, 679; cf. B.P. 713,833).

1 : 1-*Dibutoxy*-3-*ethoxypropane*. A mixture of β-ethoxypropaldehyde (124 g.) (prepared by the method of Heyse and I.G. Farbenind., G.P. 554,949; cf. Part V) and *n*-butanol (500 ml.) containing concentrated sulphuric acid (1 ml.) and calcium chloride (5 g.) was kept for 10 days at room temperature, treated with calcium oxide (10 g.), and kept for 2 days with occasional agitation. After addition of calcium chloride (15 g.) the mixture was filtered and fractionated, giving, besides unchanged starting materials, pure 1 : 1-*dibutoxy*-3-*ethoxypropane* (195 g., 70%), b. p. 122°/11 mm., 96°/0·5 mm., n_D^{20} 1·4207 (Found: C, 67·2; H, 12·15. $C_{13}H_{28}O_3$ requires C, 67·2; H, 12·15%).

Hydrolysis of this acetal (2·5 g.) with water (25 ml.) containing concentrated hydrochloric acid (10 drops) at room temperature (10 min.; shaking) and subsequent addition of 2 : 4-dinitrophenylhydrazine (2 g.) in dilute methanolic sulphuric acid gave β-ethoxypropaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 85° (identical with authentic material). This proved that no cross-etherification occurred under the mild conditions used for the preparation of the acetal.

3-*Butoxy*-1 : 1-*diethoxypropane*. A solution of β-butoxypropaldehyde (92 g.; cf. Part V) in ethanol (450 ml.) containing anhydrous hydrogen chloride (1 g.) and calcium chloride (5 g.) was kept at room temperature for 72 hr., then neutralised (sodium ethoxide in ethanol), and rapidly distilled. Fractionation of the high-boiling portion of the distillate gave, besides starting

materials, 3-*butoxy*-1 : 1-*diethoxypropane* (100 g., 70%), b. p. 100°/10 mm., n_D^{20} 1·4141 (Found : C, 65·0; H, 11·55. $C_{11}H_{24}O_3$ requires C, 64·7; H, 11·85%).

Hydrolysis of this acetal with dilute hydrochloric acid and treatment of the hydrolysate with 2 : 4-dinitrophenylhydrazine reagent as described above gave β-butoxypropaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 72°, identical with that described in Part V.

1 : 1 : 3-*Triacetoxypropane* (cf. Smith and Shell Development Co., U.S.P. 2,471,391). Acraldehyde (4 moles; containing 4—5% w/w of water) was added below 40° during 30 min. to a stirred solution of sulphuric acid (0·5 g.) in acetic anhydride (500 g.). When addition was complete the mixture was kept at 40° for 4 hr., diluted with acetic acid (1820 g.), and kept at 50° overnight. After treatment with sodium acetate (1 g.) the mixture was rapidly distilled at progressively reduced pressure, three main cuts being taken : the first, b. p. below 60°/60 mm. was acetic acid; the second cut, b. p. 65°/60 mm. to 82°/9 mm., on fractionation gave acraldehyde diacetate (3 : 3-diacetoxyprop-1-ene) (47%), b. p. 71°/10·5 mm., n_D^{20} 1·4204 (Evans and Shell Development Co., B.P. 596,620, give b. p. 85—88°/20 mm.); the third cut, b. p. 82°/9 mm. to 160°/0·2 mm., on fractionation gave pure 1 : 3-diacetoxypropene (9%), b. p. 56°/0·3 mm., n_D^{20} 1·4422 (Found : C, 53·55; H, 6·6. Calc. for $C_7H_{10}O_4$: C, 53·15; H, 6·35%), and pure 1 : 1 : 3-triacetoxypropane (9·5%), b. p. 90°/0·3 mm., n_D^{20} 1·4270. Smith, Norton, and Shell Development Co. (B.P. 638,763) gave b. p. 82°/5 mm., and 91—92°/10 mm., n_D^{20} 1·4384, for the 1 : 3-diacetoxypropene (the lower n_D^{20} might be due to the presence of different proportions of geometrical isomers or to contamination); and Smith, Norton, and Shell Development Co. (B.P. 655,040) gave b. p. 90—98°/0·6 mm., 100—101°/0·8 mm., n_D^{20} 1·4270, for 1 : 1 : 3-triacetoxypropane. [Some of these constants were also recorded by Smith, Norton, and Ballard (*J. Amer. Chem. Soc.*, 1951, **73**, 5282) after the present work had been completed.] The occurrence of the 1 : 3-diacetoxypropene in the products was, perhaps, surprising as no 1 : 3-dialkoxypropene was formed in the analogous preparation of trialkoxypropanes; the same observation was, however, subsequently made by Smith *et al.* (*loc. cit.*).

Hydrolysis of the 1 : 1 : 3-triacetoxypropane (1 g.) with water (15 ml.) containing concentrated hydrochloric acid (1 ml.) at room temperature (10 min.; shaking) and subsequent addition of 2 : 4-dinitrophenylhydrazine (1 g.) dissolved in methanol (30 ml.) containing sulphuric acid (1·5 ml.) gave, after 30 min. at room temperature, β-acetoxypropaldehyde 2 : 4-dinitrophenylhydrazone, which, crystallised from methanol, had m. p. 124—124·5° (Ballard, Geyer, Mortimer, and Shell Development Co., U.S.P. 2,467,876, give m. p. 124·5—125·5°). Smith *et al.* (*loc. cit.*) subsequently reported that the triacetoxy-compound gave acraldehyde 2 : 4-dinitrophenylhydrazone on treatment with acid and 2 : 4-dinitrophenylhydrazine.

Similar hydrolysis of 1 : 3-diacetoxypropene, n_D^{20} 1·4422, except that less hydrochloric acid was used (3 drops) gave the same 2 : 4-dinitrophenylhydrazone, m. p. 123·5—124°, and a trace of acraldehyde 2 : 4-dinitrophenylhydrazone, m. p. 166—166·5°.

Homogeneous Vapour-phase Reactions Catalysed by Diisopropyl Sulphate.—Apparatus. The apparatus consisted of a Pyrex glass tube, inclined to the horizontal at an angle of about 15° and heated by a tubular furnace, 2·5 ft. in length, the ends of which were plugged with asbestos wool. The furnace temperature was measured by means of a calibrated thermocouple inserted in the annular space between the reaction tube and the furnace. Several glass tubes were available and their different diameters (from 3/16 to 1 in.) provided one means of varying the contact time of the reactants. The glass tube was provided at the feed end with a gas inlet and with a side-arm for the liquid feed. The liquid was actually vapourised in the hot zone of the tube as no pre-heater was used. The feed-rate was controlled and kept constant by a modified Mariotte feed, and the flow-rate of the diluent gas (nitrogen) was measured by means of a directly calibrated capillary flowmeter and adjusted and kept constant by needle-valves. From the known feed rates and the volume of the hot zone, the contact time was calculated.

The product was condensed in a water-cooled coil condenser to which was attached a two-necked flask containing about 0·1—0·5 g. of quinol; the exit, from the other neck of this receiver, led through another condenser into a trap cooled by solid carbon dioxide–acetone. Loss of volatile reaction product was thus avoided.

Method and working-up. In a typical run quinoline (7·2 g., 3 mole-%) and then di*iso*propyl sulphate (0·34 g., 0·1 mole-%) were added to 1 : 1 : 3-triethoxypropane (327 g., 1·86 moles). This feed material was dropped at a constant rate (about 45 ml. per hr.) into a reaction tube (vol. of heated zone : 350 ml.) kept at 350° ± 5°. The flow of diluent nitrogen was 4·9 l. per hr. (measured at room temperature; *i.e.*, 10·8 l. per hr. at 350°). The contact (or residence) time was, therefore, about 56 sec. at the operating temperature.

The run was interrupted after 7·5 hr., when 330 ml. (295 g.) of feed had been added. The

product (containing 0·5 g. of quinol) was fractionally distilled under reduced pressure in an atmosphere of nitrogen, through a glass column (40 cm. long × 2·5 cm. int. diam.) packed with glass helices and provided with a heated jacket and a total-reflux, variable take-off head. In some distillations a column (48 cm. long × 3 cm. int. diam.) packed with stainless-steel gauze Lessing rings (1/8 × 1/8 in.) was used.

This fractionation gave: (i) ethanol (58 g.), b. p. 26°/68 mm., n_D^{20} 1·364—1·365 (lit., 1·362; therefore slightly impure); (ii) acraldehyde diethyl acetal (76·5 g.), b. p. 55°/61 mm., n_D^{20} 1·4015; (iii) 1 : 3-diethoxypropene (73·5 g.), b. p. 47—48°/12 mm., n_D^{20} 1·4230; (iv) unchanged 1 : 1 : 3-triethoxypropane (50 g., 17%), b. p. 68°/11 mm., n_D^{20} 1·4068, and a residue (18 g.); distillation loss thus amounted to 19 g. (hold-up; loss of low-boiling materials). The molar efficiency of formation of products, based on the amount of starting material consumed, was: ethanol 94%, acetal 44%, and 1 : 3-diethoxypropene 42%.

Results.—The unsaturated products derived from the various 1 : 1 : 3-trialkoxypropanes are shown in Table 8.

TABLE 8. *Pyrolysis of* 1 : 1 : 3-*trialkoxypropanes.* [a]

			Starting material $R^1O{\cdot}CH_2{\cdot}CHR^2{\cdot}CH(OR^3)_2$		Products			
					$CH_2{:}CR^2{\cdot}CH(OR^3)_2$		$R^1O{\cdot}CH_2{\cdot}CR^2{:}CH{\cdot}OR^3$ [c]	
R^1	R^2	R^3	B. p./mm.	n_D^{20}	B. p./mm.	n_D^{20}	B. p./mm.	n_D^{20}
Me	H	Me	94—95°/142	1·4003	87·5—88°/750 [d]	1·3962 [d]	64°/98	1·4202
Et	H	Et	69—70°/10 [a,b]	1·4066 [a,b]	55°/67 [b]	1·4012 [b]	55°/18 mm.	1·4238
Pr[n]	H	Pr[n]	109°/12 [a,b]	1·4175 [a,b]	52—53°/12·5 [b]	1·4120 [b]	73°/12	1·4287
Pr[i]	H	Pr[i]	89—91°/11 [a,b]	1·4096 [a,b]	38·5°/12 [d]	1·4053	62·5°/12	1·4225
Bu[n]	H	Bu[n]	123°/4 [a,b]	1·4257 [a,b]	83°/9 [b]	1·4204 [b]	110°/16	1·4348
Et	H	Bu[n]	122°/11	1·4207	85—86°/10 [e]	1·4210 [e]	80—80·5°/10 [e]	1·4286
Bu[n]	H	Et	100°/10	1·4141	— [f]	—	72·5—74°/10 [f]	1·4296
Et	Me	Et	75°/11·5 [a,b]	1·4083 [a,b]	32°/12 [b]	1·4083 [b]	54°/14	1·4259

[a] Cf. Bellringer *et al.*, *J. Appl. Chem.*, 1954, **4**, 679. [b] Cf. Part V; *J.*, 1954, 3388. [c] The acraldehyde dimethyl acetal was obtained initially as a methanol azeotrope, b. p. 31°/180 mm., n_D^{20} 1·3618, approx. 1 : 1 (acetal determined by oximation). Refractionation of the azeotrope at 1 atm. gave a lower-boiling mixture of methanol and acetal, b. p. 63°/750 mm., n_D^{20} 1·3580, and some pure acetal (for constants, see Table; Wohl and Momber, *Ber.*, 1914, **47**, 3349, give b. p. 86°/760 mm.). Alternatively, the original azeotrope was diluted with saturated aqueous sodium chloride and the upper layer separated, dried, and fractionated; it consisted largely of the acetal. [d] Myers, Magerlein, Staffen, and the Upjohn Co. (B.P. 713,088) subsequently gave b. p. 68·5—69·5°/50 mm. [e] The fractionation of the pyrolysis products gave: (i) somewhat impure ethanol, b. p. below 50°/67 mm., n_D^{20} 1·364—1·368, (ii) impure butanol (containing some ethanol), b. p. 57°/67 mm., n_D^{20} 1·391—1·398, (iii) 1-butoxy-3-ethoxyprop-1-ene (see Table), (iv) acraldehyde dibutyl acetal (see Table), and (v) unchanged starting material. Intermediate fractions are neglected; quinoline distilled between fractions (iv) and (v). [f] The fractionation of the pyrolysis products gave: (i) slightly impure ethanol, b. p. 26—30°/65 mm., n_D^{20} 1·368, (ii) a small fraction containing butanol and acraldehyde diethyl acetal, b. p. *ca.* 35°/17 mm., n_D^{20} 1·399—1·403, (iii) 3-butoxy-1-ethoxyprop-1-ene (see Table), and (iv) unchanged starting material. [g] Mixed stereoisomers.

The acraldehyde acetals were each characterised by hydrolysis and preparation of the 2 : 4-dinitrophenylhydrazone of the parent acraldehyde (m. p. and mixed m. p.). They all showed a characteristic infrared absorption peak at about 938 cm.$^{-1}$. *Acraldehyde diisopropyl acetal* was a new compound when prepared (Found: C, 68·0; H, 11·65. $C_9H_{18}O_2$ requires C, 68·3; H, 11·45%); it was subsequently described (b. p. 68·5—69·5°/50 mm.), but not analysed, by Myers, Magerlein, Staffen, and the Upjohn Co. (B.P. 713,088). On hydrogenation in ethanol (60 ml.) over Raney nickel (7·5 g. of " paste ") it (15·8 g.) gave propaldehyde di*iso*propyl acetal, b. p. 144°/752 mm., n_D^{20} 1·3995 (Adams and Adkins, *J. Amer. Chem. Soc.*, 1925, **47**, 1358, give b. p. 146·5°).

The 1 : 3-dialkoxypropenes were all new compounds (see Table 9). They had characteristic infrared absorption peaks at about 746, 938, and 1660—1665 cm.$^{-1}$. On hydrolysis with dilute acid (cf. analogous reaction of 1 : 3-diacetoxypropene) and treatment of the hydrolysate with 2 : 4-dinitrophenylhydrazine reagent they gave the corresponding β-alkoxypropaldehyde 2 : 4-dinitrophenylhydrazone (see Table 9). Hydrogenation over Raney nickel at atmospheric temperature and pressure (for conditions see Table 10) resulted in the absorption of 1 mol. of hydrogen and formation of the corresponding 1 : 3-dialkoxypropanes which are listed in Table 11.

Reaction of 1 : 3-*Diethoxypropene with Ethanol.*—Addition of 1 : 3-diethoxypropene (13 g.) in ethanol (13 g.) to ethanol (10 g.) containing anhydrous hydrogen chloride (1 g.) resulted in

spontaneous warming; the mixture was kept at room temperature overnight, made just alkaline (litmus) with sodium ethoxide in ethanol, filtered, and distilled, giving **1 : 1 : 3**-triethoxypropane (16 g., 91%), b. p. 177°/755 mm., n_D^{20} 1·4068.

Reaction of Acraldehyde Diethyl Acetal with Ethanol.—This was described in Part V.

Pyrolysis of **1 : 1 : 3**-*Triacetoxypropane* (see Table 5).—Besides acetic acid, b. p. 22—30°/12 mm., n_D^{20} 1·372—1·380, there were obtained: (i) allylidene diacetate (**3 : 3**-diacetoxyprop-1-ene) [this had b. p. 29°/0·3 mm., n_D^{20} 1·4195, and on hydrolysis with 2N-hydrochloric acid gave acraldehyde (smell), characterised as **2 : 4**-dinitrophenylhydrazone, m. p. 166°]; and (ii) **1 : 3**-diacetoxypropene, which, as obtained from the first fractionation, had b. p. 56°/0·3 mm., n_D^{20} 1·4444 and probably contained a trace of quinoline; on re-fractionation it had n_D^{20} 1·4420, identical with the material obtained in the course of preparing **1 : 1 : 3**-triacetoxypropane.

1 : 3-Diacetoxypropene (15 g.) in ethyl acetate (60 ml.) containing Raney nickel (7·5 g. of

TABLE 9. **1 : 3**-*Dialkoxypropenes.*

1 : 3-Dialkoxypropene	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H	2 : 4-Dinitrophenylhydrazone, m. p.*
1 : 3-*Dimethoxypropene*	$C_5H_{10}O_2$	58·85, 58·5	9·8, 9·8	58·8	9·85	—
1 : 3-*Diethoxypropene*	$C_7H_{14}O_2$	64·45	10·8	64·6	10·85	84—85° [a]
1 : 3-*Dipropoxypropene*	$C_9H_{18}O_2$	68·4	11·75	68·3	11·45	99—100° [b]
1 : 3-*Diisopropoxypropene*	$C_9H_{18}O_2$	68·4	11·55	68·3	11·45	98—99° [c]
1 : 3-*Dibutoxypropene*	$C_{11}H_{22}O_2$	70·7	11·6	70·9	10·9	71—72° [d]
1-*Butoxy*-3-*ethoxypropene*	$C_9H_{18}O_2$	68·7	11·6	68·3	11·45	85° [a]
3-*Butoxy*-1-*ethoxypropene*	$C_9H_{18}O_2$	68·45	11·35	68·3	11·45	72° [d]
1 : 3-*Diethoxy*-2-*methylpropene*	$C_8H_{16}O_2$	66·45	11·35	66·6	11·2	—

* Identities confirmed by mixed m. p.s with authentic β-alkoxypropaldehyde **2 : 4**-dinitrophenylhydrazones: [a] Hall and Stern, *Chem. and Ind.*, 1950, 775 (cf. Part V); Feazel and Berl, *J. Amer. Chem. Soc.*, 1950, **72**, 2278), m. p. 85°. [b] Hall and Stern, *J.*, 1952, 4083, m. p. 100·5°. [c] Part V, m. p. 99°. [d] Part V, m. p. 72—73°.

† Precise fractionation afforded the *cis*-isomer, b. p. 45—46°/10 mm., n_D^{20} 1·4230, free from the *trans*-isomer (infrared), together with fractions enriched in the latter. The purest sample, b. p. b. p. 47—48°/10 mm., n_D^{20} 1·4239, of the *trans*-compound obtained, however, still contained about 25% of the *cis*-isomer.

TABLE 10. *Hydrogenation of* **1 : 3**-*dialkoxypropenes.*

$R^1O{\cdot}CH_2{\cdot}CR^2{:}CH{\cdot}OR^3$

R^1	R^2	R^3	(g.)	Solvent and wt. (g.)		Raney nickel "paste" (g.)	H_2 absorbed (mols.)	Pure product (g.)
Me	H	Me	8·0	MeOH	32	4	1·02	*ca.* 5 [c]
Et	H	Et	48	EtOH	280	35	0·99	46·5
Pr^n	H	Pr^n	—*	EtOH	—	—	—	—
Pr^i	H	Pr^i	12·8	EtOH	44	6·5	0·97	11·0
Bu^n	H	Bu^n	6·9	EtOH	40	5	1·01	6·5
Et	H	Bu^n	7·0	EtOAc	40	5	0·98	6·3 [b]
Bu^n	H	Et	8·6	EtOH	40	5	0·99	6·5 [b]
Et	Me	Et	18·6	EtOH	48	5	0·94	17·1

* Quantitative data not available (starting material slightly impure). [b] These hydrogenations afforded the same product, 1-butoxy-3-ethoxypropane. [c] Ether-extraction necessary to obtain pure material.

TABLE 11. **1 : 3**-*Dialkoxypropanes.*

1 : 3-Dialkoxypropane	B. p./mm.	n_D^{20}	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
1 : 3-Dimethoxypropane [a]	105—105·5°/756	1·3898	$C_5H_{12}O_2$	—	—	—	—
1 : 3-Diethoxypropane [b,c]	140—141°/750	1·3980	$C_7H_{16}O_2$	63·2	12·0	63·6	12·2
1 : 3-*Dipropoxypropane*	165°/750	1·4080	$C_9H_{20}O_2$	67·3	12·2	67·45	12·6
1 : 3-*Diisopropoxypropane*	159—160°/750	1·4015	$C_9H_{20}O_2$	67·65	12·55	67·45	12·6
1 : 3-*Dibutoxypropane*	213°/750, 97°/11	1·4170	$C_{11}H_{24}O_2$	69·8	12·95	70·15	12·85
1-*Butoxy*-3-*ethoxypropane*	182°/750	1·4100	$C_9H_{20}O_2$	67·9	12·75	67·45	12·6
1 : 3-*Diethoxy*-2-*methylpropane*	145°/750	1·4012	$C_8H_{18}O_2$	65·6	12·65	65·7	12·4

* Also obtained (b. p. 105°, n_D^{20} 1·3889), in poor yield, by Baker and Field's method (*J.*, 1932, 86) from 3-methoxypropan-1-ol (56 g.) containing sodium (4·3 g.) on methylation with methyl sulphate (60 g.) in ether (150 ml.). Baker and Field (*loc. cit.*) give b. p. 106°/753 mm. [b] d_4^{20} 0·834, $[R]_D^{20}$ 37·63 (calc. 37·81). [c] Noyes (*Amer. Chem. J.*, 1897, **19**, 768) gives b. p. 140—141°/760 mm., d_{22}^{22} 0·835; Rojahn and Lemme (*Arch. Pharm.*, 1925, **263**, 617) record b. p. 140°.

" paste," under ethyl acetate) rapidly absorbed hydrogen (1·05 mol.), and gave 1 : 3-diacetoxypropane, b. p. 207°/748 mm., n_D^{20} 1·4200 (Smith, Norton, and Ballard, *J. Amer. Chem. Soc.*, 1951, **73**, 5282, subsequently recorded b. p. 88—90°/10 mm., n_D^{20} 1·4184 and 1·4192). The use of ethanol as solvent induced side-reactions, including the formation of some ethyl acetate.

Pyrolysis of 1 : 1 : 3-*Trimethoxypropane over Alumina* (by I. K. M. Robson).—The apparatus was similar to that for the homogeneous vapour-phase experiments except that the reaction tube (1-in. diameter) was horizontal and was packed with alumina (vol. of packed zone, 245 ml.). 1 : 1 : 3-Trimethoxypropane (358·5 g.) was fed into the reaction tube at a constant rate during 2 hr. together with nitrogen (17·55 l./hr. at N.T.P.), the average reaction temperature being 228°. The bulk (301·6 g.) of the product (318·1 g.) was fractionated to give the following main fractions: (i) a mixture (224·7 g.) of acraldehyde, methanol, and acraldehyde dimethyl acetal, boiling range 38°/752 mm. to 63°/748 mm. (mainly 60—63°/748 mm.), n_D^{20} 1·3773—1·3923; (ii) acraldehyde dimethyl acetal (11·3 g.), b. p. 32—52°/100 mm., n_D^{20} 1·3973; (iii) 1 : 3-dimethoxypropene (5·4 g.), b. p. 63·5—66°/98 mm., n_D^{20} 1·4201; and (iv) a residue (23·0 g.). Intermediate fractions are neglected in the above summary.

Other Catalysed Thermal Fissions.—(1) *Vapour phase.* Miscellaneous experiments with 1 : 1 : 3-triethoxypropane designed to examine the effect of (*a*) acidic (sulphuric acid, methyl sulphate) and basic catalysts (quinoline), on the course of the reaction, and (*b*) the reaction conditions on the two products (acetal or 1 : 3-dialkoxypropene) are summarised in Tables 4 and 2, respectively.

(2) *Liquid phase.* The following experiments were performed using liquid 1 : 1 : 3-triethoxypropane and either solid or liquid catalysts: (*a*) Ammonium sulphate. 1 : 1 : 3-Triethoxypropane (79·5 g.) and powdered ammonium sulphate (0·1 g.) were refluxed in a flask attached to a fractionating column, and the products were distilled out as formed. A further portion (0·1 g.) of the catalyst was added when the reaction slowed down, and heating was continued until no more liquid remained in the flask. The distillate on fractional distillation gave ethanol (12·7 g.), acraldehyde diethyl acetal (13·8 g.), 1 : 3-diethoxypropene (19·6 g.), and unchanged 1 : 1 : 3-triethoxypropane (22·75 g.). (*b*) Fuller's earth. Fuller's earth (5 g.; No. 249) was suspended in kerosene (50 g.) and vigorously stirred at 165°; 1 : 1 : 3-triethoxypropane (100 g.) was then added slowly. The temperature was raised to 220° when addition was complete, and the products were distilled out as they were formed. They were dried (K_2CO_3), and on fractional distillation gave ethanol (40·5 g.), acraldehyde diethyl acetal (12 g.), and 1 : 3-diethoxypropene (2 g.). (*c*) Sulphuric acid. 1 : 1 : 3-Triethoxypropane (100 g.) and concentrated sulphuric acid (0·185 g.) were refluxed in a flask attached to a fractionating column, and the products were distilled as they were formed. The product on fractional distillation gave ethanol (27·55 g.), acraldehyde diethyl acetal (29·5 g.), 1 : 3-diethoxypropene (11·9 g.), and unchanged 1 : 1 : 3-triethoxypropane (12·5 g.).

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The Kinetics of Chlorohydrin Formation. Part VII. The Reaction between Hypochlorous Acid and Allyl Acetate in the Presence of Sodium Acetate–Acetic Acid Buffers of Constant* pH.

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The addition of hypochlorous acid to allyl acetate in aqueous solutions buffered by equal quantities of sodium acetate and acetic acid to pH 4·70 has been studied. It is found that, above a certain minimum concentration of the ester, the velocity of reaction conforms to the kinetic equation

$$v = k_2^{I}[HOCl][C_3H_5OAc] + (k_3^{II} + k_3^{IV}[HOAc])[HOCl]^2 + k_2^{III}[HOCl][HOAc]$$

Below this minimum concentration, which varies with the concentration of hypochlorous acid, the kinetics of the reaction appear to be varying and consequently attempts to derive a kinetic equation were unwarranted.

The values found for the constants k_3^{II}, k_2^{III}, and k_3^{IV} agree with those found previously for the reaction between hypochlorous acid and allyl alcohol under similar conditions.

The kinetics of the addition of hypochlorous acid to various mono-olefinic compounds have been found by Israel and his co-workers to be complex. Consecutive reactions are believed to occur, the end-product in each case being the chlorohydrin (cf. Israel, Martin, and Soper, *J.*, 1950, 1282; Israel, *J.*, 1950, 1286; Craw and Israel, *J.*, 1952, 550; Reeve and Israel, *J.*, 1952, 2327; Craw, *J.*, 1954, 2510, 2515). In each reaction the term $k_2^{II}[HOCl]^2$ appeared in the kinetic equation, and it has been surmised that this represents the rate of formation of chlorine monoxide from hypochlorous acid: $2HOCl \longrightarrow Cl_2O + H_2O$. The potential ease of separation of positive chlorine from chlorine monoxide has been calculated to be 10^6 times greater than that from hypochlorous acid (Reeve and Israel, *loc. cit.*), and chlorine monoxide would therefore be expected to react as fast as it is formed. It follows that the value of k_2^{II}, the specific reaction rate for the formation of chlorine monoxide, should be independent of the nature of the ethylenic compound. Table 1 shows that this is not true for crotonic acid.

Table 1. *Values of* k_2^{II} *at* pH 4·7 *at* 25°.

Compound	k_2^{II} (l. mole^{-1} min.$^{-1}$)	Observers
Allyl alcohol	8·2	Israel
Crotonic acid	4·0	Craw and Israel
Tiglic acid	7·5	Craw
ββ-Dimethylacrylic acid	10·1	Craw (personal communication)

For allyl alcohol, the kinetic terms $(k_2^{III} + k_3^{II}[HOCl])[HOCl][HOAc]$ were found. The first term has been interpreted as the rate of formation of acetyl hypochlorite by the reaction, $HOCl + HOAc \longrightarrow AcOCl + H_2O$, the acetyl hypochlorite reacting with the allyl alcohol as fast as it is formed. Thus the value of k_2^{III} should also be independent of the nature of the ethylenic substance. This supposition has not been tested.

The term $k_3^{II}[HOCl]^2[HOAc]$ has been interpreted by Israel *et al.* (*locc. cit.*) as the rate of the acid-catalysed formation of chlorine monoxide. Doubt has been thrown on this mechanism by Craw (*J.*, 1954, 2515) who found that no such term appears in the kinetic equation for tiglic acid; he suggested an alternative mechanism to account for the appearance of the term when acetic or crotonic acid is present, and for its absence in the tiglic acid reaction. (For this reason, the corresponding specific reaction rate is denoted below by k_3^{IV}.)

In an effort to throw further light on these problems, it was decided to extend studies of the reaction to allyl acetate.

* Part VI, *J.*, 1954, 2515.

Experimental

Materials.—Allyl acetate was left over crystalline ferrous ammonium sulphate for at least two days to remove any peroxides. It was then dried (Na_2SO_4) and fractionated in an all-glass apparatus. The product had b. p. 103°/760 mm., $n_D^{24.7}$ 1·4025 (Beilstein gives 103·5—104°/762·5 mm., n_D^{20} 1·40488). The 0·1M-aqueous solution of the ester was made up fresh before each series of experiments. This procedure was found to be necessary if after-blueing (unstable end-points during the titrations) was to be avoided during the rate measurements. Such after-blueing was clearly caused by the presence of peroxides in the allyl acetate, since on their removal sharp stable end-points were obtained. Solutions of the ester were found not to be appreciably hydrolysed for two days after being made up. For each series, the solutions of ester were used within 3½ hr.

Mercuric oxide was purified by dissolving it in perchloric acid and reprecipitating it with sodium hydroxide solution (de la Mare, Ketley, and Vernon, *J.*, 1954, 1290). Hypochlorous acid solution was prepared by saturating a suspension of the purified mercuric oxide in water with chlorine at about 0° and distilling the resultant mixture under reduced pressure in the dark below 35°. It kept reasonably well in dark bottles at about 0° and was diluted to the required concentration immediately before use. However, in no case was a solution used which had been kept for more than five days.

Sodium acetate–acetic acid buffer solutions were prepared from pure glacial acetic acid, pure sodium hydroxide (free from carbonate), and carbon dioxide-free water, so that the final concentration of the stock buffer solution was 0·1M with respect to acetic acid and to sodium acetate.

Kinetic Methods.—A new technique was developed in which the required volumes of the stock allyl acetate solution and of the buffer solution were treated with distilled water to make a total volume of 50 ml. To start the reaction, 50 ml. of the hypochlorous acid solution were added from a modified Stas pipette, which is fitted with a jacket through which water from the constant temperature bath was circulated. The side-arm, through which the pipette is filled, is slightly constricted at the point at which it is joined to the pipette so that drainage from the side-arm of variable quantities of solution is prevented. The flask was shaken gently during the addition of the hypochlorous acid and was removed immediately the pipette had emptied, no time being allowed for drainage. In a check series of experiments, the pipette was found to deliver 50·195, 50·205, 50·190, 50·225, 50·200 (mean 50·203 ± 0·022) g. of distilled water at 25°, the draining time being about 3·5 sec. Thus the volume of liquid delivered by the pipette was 50·25 ml. with an error less than 0·5%.

Aliquot parts (10 ml.) of the reaction mixture were removed at the appropriate times, run into acidified solutions of potassium iodide, and analysed.

All experiments were carried out at 25·00° ± 0·01°.

Rate Measurements.—Rate measurements and the determination of v_0 were carried out by the method described by Israel, Martin, and Soper (*loc. cit.*), the reaction mixture being sampled at quarter-minute or half-minute intervals. de la Mare, Ketley, and Vernon (*loc. cit.*) carried out kinetic measurements on the reaction between hypochlorous acid and phenol, mesitylene, or one of three aromatic ethers in the presence of perchloric acid and silver perchlorate, the perchlorate being present to ensure the absence of chloride and hence of free chlorine in the reaction mixture. Accordingly, experiments in which silver perchlorate was added and similar experiments without the addition of the perchlorate were carried out. The results of a typical pair of such experiments are given in Table 2.

Table 2.

$[HOCl]_0 = 4·775 \times 10^{-3}$; $[C_2H_3OAc]_0 = 5·0 \times 10^{-2}$; $[HOAc] = 5·0 \times 10^{-3}$; $[AgClO_4] = 0·127$.

Time (min.)		0·5	1·0	1·5	2·0	2·5	3·0
Titre (ml. $4·042 \times 10^{-3}$N-$Na_2S_2O_3$)	($AgClO_4$ present) ...	10·72	7·68	7·50	6·90	6·33	6·02
	($AgClO_4$ absent) ...	20·95	19·36	18·00	16·77	—	14·63

These and similar results show that the addition of silver perchlorate markedly affects the course of the reaction, approximately in proportion to the amount of silver perchlorate added even when the perchlorate is present in a concentration some twenty times greater than that of hypochlorous acid (as quoted in Table 2). On the other hand, the plot of the logarithms of the titres against time for the reaction carried out in the absence of the perchlorate was linear and

gave, on extrapolation to zero time, a value of 1·355 corresponding to an initial titre of 22·65 ml. This value agrees with the titre (22·63 ml.) of the corresponding blank experiment in which 50 ml. of the same hypochlorous acid solution were added to 50 ml. of distilled water. The latter agreement suggests that there was little likelihood of the presence of free chlorine in the solution of hypochlorous acid used, since such free chlorine would react so much faster than hypochlorous acid, chlorine monoxide, or acetyl hypochlorite (cf. Shilov *et al.*, *Trans. Inst. Chem. Tech. Ivanovo*, **1935**, **19**; *J. Phys. Chem. Russia*, 1934, **5**, 654; **1936**, **8**, 909; **1937**, **10**, 123; 1939, **13**, 759, 1242). It appears that addition of silver perchlorate catalyses the decomposition of hypochlorous acid under our conditions. Therefore, all our experiments were carried out without perchlorate.

To ensure that the stock hypochlorous acid solutions used had not decomposed appreciably and thus contained no free chlorine, a blank experiment was carried out in conjunction with each series of experiments. If the concentration in this blank run was appreciably greater than the initial concentration determined from the rate curves, the difference was assumed to be due to the presence of free chlorine and the results were rejected.

Results

Variation of the Initial Concentration of the Ester.—The plot of the reaction velocity against the initial concentration of the ester, with constant initial concentration of the buffer, was linear only above a certain minimum ester concentration. The value of this minimum varied with the initial concentration of hypochlorous acid but in no case investigated was less than $[C_2H_5OAc]_0 = 2{\cdot}5 \times 10^{-3}$. The results obtained on using concentrations of the ester greater than this minimum are given in Table 3.

Table 3. $10^3[HOAc] = 5{\cdot}0$ *mole l.*$^{-1}$

10^3[HOCl] (mole l.$^{-1}$)	10^3[C_2H_5OAc] (mole l.$^{-1}$)	10^5v_0 (mole l.$^{-1}$ min.$^{-1}$) (obs.)	(calc.)	10^3[HOCl] (mole l.$^{-1}$)	10^3[C_2H_5OAc] (mole l.$^{-1}$)	10^5v_0 (mole l.$^{-1}$ min.$^{-1}$) (obs.)	(calc.)
1·078	3	9·61	9·53	3·229	3	39·51	39·85
	4	9·86	9·75		4	40·25	40·49
	5	10·01	9·96		5	41·01	41·14
	7	10·42	10·39		7	42·24	42·43
	9	10·85	10·82		9	43·74	43·72
1·846	4	19·13	19·00	4·303	3	60·45	60·60
	5	19·48	19·37		4	61·15	61·46
	6	19·85	19·74		5	62·15	62·32
	7	20·19	20·10		7	63·72	64·04
	8	20·68	20·41		9	65·40	65·77
2·755	3	31·74	31·87				
	4	32·26	32·42				
	6	33·32	33·53				
	7	33·95	34·08				
	8	34·47	34·63				

Analysis of the observed values of v_0 by the method of least squares shows that they conform to the equation

$$v_0 = v_{res.} + k[C_2H_5OAc] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The values of $v_{res.}$ and k so obtained are given in Table 4, from which it is clear that k is proportional to the concentration of hypochlorous acid, *i.e.*,

$$k = k_2^{I}[HOCl]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Table 4.

10^3[HOCl]$_0$ (mole l.$^{-1}$)	$10^5v_{res.}$ (mole l.$^{-1}$ min.$^{-1}$)	10^3k (min.$^{-1}$)	k_2^{I} (l. mole^{-1} min.$^{-1}$)	k_2^{II} (l. mole^{-1} min.$^{-1}$)
1·08	9·01	0·203	0·19	9·12
1·85	17·58	0·381	0·21	8·28
2·76	30·07	0·549	0·20	7·91
3·23	37·46	0·695	0·22	7·70
4·30	57·92	0·831	0·19	8·07
			Mean 0·20	8·22

The plot of $v_{res.}/[HOCl]_0$ varied linearly with $[HOCl]_0$ and could be represented by

$$v_{res.}/[HOCl]_0 = k_1 + k_2[HOCl]$$

or

$$v_{res.} = k_1[HOCl]_0 + k_2[HOCl]_0^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $10^3k_1 = 6{\cdot}61$ min.$^{-1}$ and $k_2 = 15{\cdot}74$ l. mole^{-1} min.$^{-1}$.

Variation of the Concentration of the Acetate Buffer.—This variation was examined at constant concentrations of the ester, the results being given in Tables 5 *A*—*E*.

TABLE 5.

10^3[HOCl] (mole l.$^{-1}$)	10^3[HOAc] (mole l.$^{-1}$)	10^5v_0 (mole l.$^{-1}$ min.$^{-1}$) (obs.)	(calc.)	10^3[HOCl] (mole l.$^{-1}$)	10^3[HOAc] (mole l.$^{-1}$)	10^5v_0 (mole l.$^{-1}$ min.$^{-1}$) (obs.)	(calc.)
		(*A*) $10^2[C_3H_5OAc] = 3{\cdot}0$ mole l.$^{-1}$.					
1·620	2	8·12	8·17	3·203	2	22·13	20·92
	4	13·18	13·23		4	34·31	33·57
	6	18·23	18·29		6	45·92	45·23
	8	23·28	23·35		8	56·80	54·88
	10	28·33	28·41		10	69·34	68·53
1·835	2	9·60	9·70	3·702	2	28·14	27·43
	4	15·52	15·56		4	41·13	41·49
	6	21·28	21·42		6	55·55	55·56
	8	27·21	27·29		8	70·78	69·62
	10	33·13	33·15		10	84·41	83·69
2·026	2	11·08	11·15	4·728	2	40·61	39·54
	4	17·66	17·74		4	59·33	60·07
	6	24·24	24·34		6	78·93	79·60
	8	30·82	30·93		8	98·22	99·13
	10	37·40	37·53		10	118·20	118·66
2·809	2	17·82	17·96				
	4	27·65	27·82				
	6	37·48	37·68				
	8	47·31	47·54				
	10	57·13	57·40				
		(*B*) $10^2[C_3H_5OAc] = 4{\cdot}0$ mole l.$^{-1}$.					
0·919	2	4·07	4·08	3·068	2	20·98	21·13
	4	6·73	6·75		4	31·97	32·16
	6	9·38	9·41		6	42·96	43·19
	8	12·04	12·07		8	53·95	54·21
	10	14·70	14·71		10	64·94	65·24
1·537	2	7·87	7·91	3·808	2	29·19	29·43
	4	12·62	12·66		4	43·73	44·03
	6	17·37	17·42		6	58·27	58·63
	8	22·13	22·18		8	72·83	73·23
	10	26·88	26·94		10	87·35	87·83
2·311	2	13·80	13·92				
	4	21·49	21·66				
	6	29·17	29·39				
	8	36·86	37·13				
	10	44·55	44·87				
		(*C*) $10^2[C_3H_5OAc] = 5{\cdot}0$ mole l.$^{-1}$.					
0·818	2	3·69	3·70	3·386	2	—	25·23
	4	6·03	6·04		4	37·51	37·75
	6	8·37	8·38		6	49·99	50·27
	8	10·71	10·73		8	62·46	62·79
	10	13·06	13·07		10	74·94	75·30
1·729	2	9·55	9·62	4·195	2	34·77	35·11
	4	14·99	15·08		4	51·29	51·72
	6	20·44	20·54		6	67·82	68·33
	8	25·87	26·00		8	84·35	84·93
	10	31·32	31·47		10	100·87	101·54
2·527	2	16·25	16·36	4·499	2	38·83	39·22
	4	24·87	25·00		4	57·12	57·49
	6	33·48	33·65		6	75·43	75·76
	8	42·09	42·29		8	93·37	94·03
	10	50·71	50·93		10	111·40	112·30
2·679	2	17·70	17·79				
	4	26·80	27·08				
	6	36·00	36·37				
	8	45·10	45·66				
	10	54·73	54·94				

TABLE 5. (*Continued.*)

(*D*) $10^2[C_2H_5OAc] = 6{\cdot}0$ mole l.$^{-1}$.

1·523	2	8·38	8·42	3·039	2	22·17	22·03
	4	13·08	13·13		4	32·90	32·91
	6	17·79	17·84		6	43·62	43·79
	8	22·49	22·56		8	55·29	54·67
	10	27·19	27·29		10	65·79	65·61
2·280	2	14·53	14·63	3·799	2	30·34	30·83
	4	22·14	22·31		4	45·78	45·37
	6	29·74	29·96		6	59·50	59·91
	8	37·35	37·61		8	74·66	74·45
	10	44·95	45·26		10	88·37	89·06
2·675	2	18·01	18·30				
	4	27·33	27·57				
	6	36·59	36·84				
	8	45·92	46·11				
	10	56·36	55·39				

(*E*) $10^2[C_2H_5OAc] = 7{\cdot}0$ mole l.$^{-1}$.

1·021	2	5·20	5·27	3·063	2	22·67	22·91
	4	8·25	8·26		4	33·71	33·91
	6	11·24	11·25		6	44·77	44·91
	8	14·20	14·24		8	55·58	55·91
	10	17·19	17·24		10	66·64	66·91
1·781	2	10·67	10·73	3·558	2	28·73	28·60
	4	16·29	16·39		4	41·38	41·95
	6	22·03	22·05		6	55·07	55·30
	8	27·61	27·70		8	68·25	68·65
	10	33·44	33·36		10	81·53	82·00
2·082	2	13·23	13·26	4·134	2	35·68	35·97
	4	19·81	20·08		4	51·96	52·21
	6	26·90	26·90		6	68·14	68·53
	8	33·76	33·72		8	84·31	85·81
	10	40·42	40·54		10	—	101·09

For definite values of the concentrations of ester and of hypochlorous acid, it was found that the results could be represented by equations of the type :

$$v_0 = v'_{res.} + k'[HOAc] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The values of $v'_{res.}$ and k' determined by the method of least squares are given in Table 6.

TABLE 6.

$10^2[C_2H_5OAc]_0$ (mole l.$^{-1}$)	$10^2[HOCl]_0$ (mole l.$^{-1}$)	$10^5v'_{res.}$ (mole l.$^{-1}$ min.$^{-1}$)	$10^2k'$ (min.$^{-1}$)	$10^2[C_2H_5OAc]_0$ (mole l.$^{-1}$)	$10^2[HOCl]_0$ (mole l.$^{-1}$)	$10^5v'_{res.}$ (mole l.$^{-1}$) min.$^{-1}$)	$10^2k'$ (min.$^{-1}$)
3·0	1·62	3·07	2·53	6·0	1·52	3·68	2·35
	1·84	3·73	2·94		2·28	6·92	3·80
	2·03	4·50	3·29		2·68	8·25	4·77
	2·81	7·99	4·91		3·04	11·03	5·43
	3·20	10·63	5·85		3·80	16·10	7·24
	3·70	13·34	7·11	7·0	1·02	2·24	1·50
	4·73	20·84	9·70		1·78	4·95	2·84
4·0	0·92	1·41	1·33		2·08	6·33	3·42
	1·54	3·12	2·38		3·06	11·74	5·49
	2·31	6·11	3·84		3·56	15·25	6·62
	3·07	9·99	5·50		4·13	19·51	8·10
	3·81	14·65	7·27				
5·0	0·82	1·35	1·17				
	1·73	4·11	2·72				
	2·53	7·64	4·31				
	2·68	8·36	4·62				
	3·39	12·55	6·24				
	4·20	18·24	8·26				
	4·50	20·82	9·07				

For each concentration of the ester, plots of $k'/[HOCl]_0$ and $v'_{res.}/[HOCl]_0$ against $[HOCl]_0$ were linear. Thus k' and $v'_{res.}$ could be represented by

$$v'_{res.} = k_1^{I}[HOCl]_0 + k_2^{II}[HOCl]_0^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and

$$k' = k_2^{III}[HOCl]_0 + k_3^{IV}[HOCl]_0^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The values of the four constants k_1^{I}, k_2^{II}, k_2^{III}, and k_3^{IV} obtained by the method of least squares are given in Table 7 from which it is clear that k_2^{II}, k_2^{III}, and k_2^{IV} are reasonably constant and that k_1^{I} is directly proportional to the concentration of the ester, *i.e.*,

$$k_1^{I} = k_2^{I}[C_3H_5OAc]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The value of k_2^{I} so obtained is in excellent agreement with the mean value quoted in Table 4.

TABLE 7.

$10^3[C_3H_5OAc]_0$	k_1^{I} (min.$^{-1}$)	k_2^{I} (l. mole^{-1})	k_2^{II} (l. mole^{-1} min.$^{-1}$)	k_2^{III} (l. mole^{-1} min.$^{-1}$)	$10^{-3}k_3^{IV}$ (l.^{2} mole^{-2} min.$^{-1}$)
3·0	0·564	0·19	8·22	13·0	1·63
4·0	0·803	0·20	7·99	13·0	1·61
5·0	0·975	0·20	8·08	13·0	1·60
6·0	1·240	0·21	7·69	12·8	1·73
7·0	1·337	0·19	8·20	13·2	1·54
Mean	——	0·20	8·04	13·0	1·62

Combination of equations (4), (5), (6), and (7), gives the complete velocity equation

$$v_0 = k_2^{I}[HOCl]_0[C_3H_5OAc]_0 + k_2^{II}[HOCl]_0^2 + k_2^{III}[HOCl]_0[HOAc] + k_3^{IV}[HOCl]_0^2[HOAc] \quad . \quad (8)$$

That this provides a satisfactory representation of the course of the reaction has been confirmed in three ways.

(*a*) Combination of equations (1), (2), and (3) and substitution of the values of the relevant constants gives

$$v_0 = 0{\cdot}20[HOCl]_0[C_3H_5OAc]_0 + 6{\cdot}61 \times 10^{-3}[HOCl]_0 + 15{\cdot}74[HOCl]_0^2 \quad . \quad . \quad (9)$$

as the velocity equation for constant $[HOAc] = 5 \times 10^{-3}$.

Comparison with equation (8) shows that

$$k_2^{III}[HOAc] = 6{\cdot}61 \times 10^{-3} \text{ when } [HOAc] = 5 \times 10^{-3}$$

i.e.,

$$k_2^{III} = 13{\cdot}2 \text{ l. mole}^{-1} \text{ min.}^{-1}$$

Also,

$$k_2^{II} + k_3^{IV}[HOAc] = 15{\cdot}74 \text{ when } [HOAc] = 5 \times 10^{-3}$$

Substitution of the mean value of k_3^{IV} from Table 7 thus gives $k_2^{II} = 7{\cdot}64$ l. mole^{-1} min.$^{-1}$.

The values of k_2^{II} and k_2^{III} so obtained are in good agreement with those quoted in Table 7.

(*b*) From a statistical point of view, analysis of the results quoted in Table 6 would be expected to give a more reliable value for the constant k_2^{III} than that obtained from equation (9). Therefore, it is probably more satisfactory to substitute the mean values of k_2^{III} and k_3^{IV} from Table 7 into the equation

$$v_{res.} = k_2^{II}[HOCl]_0^2 + k_2^{III}[HOCl]_0[HOAc] + k_3^{IV}[HOCl]_0^2[HOAc] \quad . \quad . \quad (10)$$

[which follows by combining equations (1), (2), and (8)] to obtain the value of k_2^{II}. The resultant values for this constant are shown in column 5 in Table 4. When it is remembered that this procedure tends to cause the accumulation of experimental errors in the corresponding values of k_2^{II}, the results show a reasonable constancy and the mean value of this constant is in good agreement with that quoted in Table 7. The overall mean value of k_2^{II} is thus found to be 8·13 l. mole^{-1} min.$^{-1}$.

(*c*) Substitution of the values of the four constants in equation (8) gives the velocity equation

$$v_0 = 0{\cdot}20[HOCl]_0[C_3H_5OAc]_0 + 8{\cdot}13[HOCl]_0^2 + 13{\cdot}0[HOCl]_0[HOAc] + 1{\cdot}62 \times 10^3[HOCl]_0^2[HOAc] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Equation (11) was used to calculate the values of v_0 given in column 4 in each of Tables 3 and 5 *A*—*E* from which it is clear that there is a satisfactory agreement between the observed and the calculated values of v_0.

DISCUSSION

The form of the derived kinetic equation is identical with that reported earlier, the values of the constants k_2^{II}, k_2^{III}, and k_3^{IV} being in reasonable agreement (Table 8).

TABLE 8.

Ethylenic compound	k_2^{II} (l. mole^{-1} min.$^{-1}$)	k_2^{III} (l. mole^{-1} min.$^{-1}$)	k_3^{IV} (l.^{2} mole^{-2} min.$^{-1}$)
Allyl alcohol	8·2	14·5	1·56
Allyl acetate	8·13	13·0	1·62

However, it was observed during this investigation that presence of traces of chlorine affected the values of the derived constants seriously. For this reason, great care was taken to ensure that the hypochlorous acid solutions used contained no free chlorine. The differences in the values of the constants quoted in Tables 1 and 8 may well be due to the interference of traces of chlorine. We propose to investigate this further.

Nevertheless, the agreement obtained provides strong evidence that the interpretations of the terms k_2^{II}[HOCl]^2 and k_2^{III}[HOCl][HOAc] given by Israel (*loc. cit.*) are correct. The interpretation of k_3^{IV}[HOCl]^2[HOAc] given by Craw (*loc. cit.*) appears to be the more plausible, although we have obtained no evidence for this view in this investigation.

The value of k_2^{I} (0·20) is approximately one-tenth of the corresponding value found for allyl alcohol (1·98, Israel, *loc. cit.*). This is to be expected since allyl acetate would be much less reactive than the corresponding alcohol in view of the deactivating effect of the acetyl group due to its tendency to withdraw electrons from the ethylenic bond.

We acknowledge the continued encouragement and interest of Professor J. E. Driver and record our appreciation to Mr. A. J. Berry who supplied us with the details of the Stas pipette.

UNIVERSITY OF HONG KONG, HONG KONG. [*Received, January 27th*, 1955.]

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*The Kinetics of Alkyl–Oxygen Fission in Ester Hydrolysis. Part III.** tert.*-Butyl Benzoate in Aqueous Acetone.*

By V. R. STIMSON.

[Reprint Order No. 6235.]

The kinetics of the acid-catalysed hydrolysis of *tert.*-butyl benzoate in aqueous acetone have been studied. The Arrhenius parameters E and A are different from those found for hydrolysis by mechanism $A_{AC}2$ but are like those found for the hydrolysis of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate (Part II *). It is suggested that these results are due to the operation of mechanism $A_{AL}1$.

Two mechanisms for the acid-catalysed hydrolysis of *tert.*-butyl benzoate in aqueous solvents are inherently likely, namely, $A_{AC}2$ and $A_{AL}1$. Changes in R of R'·CO·OR do not greatly affect the rate of hydrolysis by $A_{AC}2$ but in general the rate is slightly decreased by an increase in the number of alkyl groups on the alkyl carbon atom (Timm and Hinshelwood, *J.*, **1938**, 869; Newling and Hinshelwood, *J.*, **1936**, 1358; Hammett, "Physical Organic Chemistry," McGraw-Hill, 1940, p. 213), whereas *tert.*-alkyl acetates and succinates are hydrolysed more rapidly than are the primary alkyl esters (Skrabal, *Monatsh.*, 1926, **47**, 17; Homan, *Rec. Trav. chim.*, 1944, **63**, 181). The rate by mechanism $A_{AL}1$ is expected to be influenced largely by R and very little by R' (Day and Ingold, *Trans. Faraday Soc.*, **1941**, **37**, 686). Hence, for *tert.*-butyl benzoate the rate of hydrolysis by $A_{AC}2$ should be comparable with, or perhaps slightly smaller than, that of ethyl benzoate for which $\log_{10} 10^6 k_{100}$ (sec.$^{-1}$) = 1·97 in 60% acetone (Timm and Hinshelwood, *loc. cit.*), and by $A_{AL}1$ comparable with that of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate for which this figure is 4·1 (Part II *), so that this ester should be hydrolysed mainly if not wholly by $A_{AL}1$. For uncatalysed alcoholysis Cohen and Schneider (*J. Amer. Chem. Soc.*, **1941**, **63**, 3382) have shown that alkyl–oxygen fission is involved, and Bunton has also established this for the acid-catalysed reaction (Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, **1953**, p. 780). The present work shows that the hydrolysis

* Part II, *J.*, 1955, 2010.

of *tert.*-butyl benzoate has kinetic features unlike those found for hydrolysis by $A_{AC}2$ but very like those found in the case of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate for which only $A_{AL}1$ is likely, and it is suggested that these features are characteristic of mechanism $A_{AL}1$.

First-order rate constants (k_1) for the hydrolysis of tert.*-butyl benzoate in aqueous acetone.*

(C_A and C_E are the concentrations, in moles/l., of hydrochloric acid and ester, respectively.)

Acetone (% by vol.)	Temp.	10^3C_A	10^3C_E	10^3k_1 (min.$^{-1}$)	$10k_1/C_A$ (min.$^{-1}$ l. mole^{-1})	Acetone (% by vol.)	Temp.	10^3C_A	10^3C_E	10^3k_1 (min.$^{-1}$)	$10k_1/C_A$ (min.$^{-1}$ l. mole^{-1})
50	97·1°	1·17	1·78	11·2	9·6	60	,,	0·68	2·74	4·7	6·9
60	97·1	2·10	3·45	13·3	6·4	,,	,,	0·38	2·19	2·7	7·1
,,	,,	1·49	1·82	10·3	6·9	,,	84·3°	1·09	2·06	1·82	1·67
,,	,,	1·19	1·70	7·9	6·6	,,	71·2	1·56	1·87	0·53	0·34
,,	,,	1·13	1·47	7·9	7·0	80	97·1	1·13	1·58	4·6	4·1
,,	,,	1·10	2·16	7·1	6·5	,,	84·3	1·10	2·08	1·04	0·95
,,	,,	1·09	3·71	7·4	6·8	90	97·1	1·14	1·86	3·8	3·3
,,	,,	0·83	2·09	5·6	6·8	95	97·1	1·45	1·83	5·3	3·7

Experimental.—tert.-Butyl benzoate (preparation by Mr. E. J. Watson) (Found : C, 73·9; H, 7·9. Calc. for $C_{11}H_{14}O_2$: C, 74·0; H, 7·9%), prepared by the method of Norris and Rigby (*J. Amer. Chem. Soc.*, **1932**, **54**, 2099), who report b. p. 96°/2 mm. n_D^{25} 1·4896, had b. p. 50°/0·5 mm., n_D^{24} 1·4900. Pfannl (*Monatsh.*, **1911**, **32**, 513) reports b. p. 94°/10 mm. and Bender (*J. Amer. Chem. Soc.*, **1951**, **73**, 1626) gives b. p. 67—68°/1 mm., n_D^{25} 1·4890. The purity, calculated from the titre on complete hydrolysis, was 99·5%. The experimental procedure has been described in Parts I (*J.*, 1954, 2848) and II (*loc. cit.*).

Results and Discussion

The hydrolysis of *tert.*-butyl benzoate in aqueous acetone accurately follows first-order kinetics and the rate constants (k_1) are proportional to the concentration of the acid catalyst

Fig. 1.

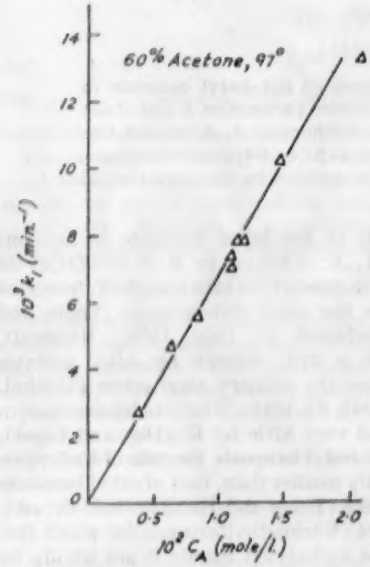
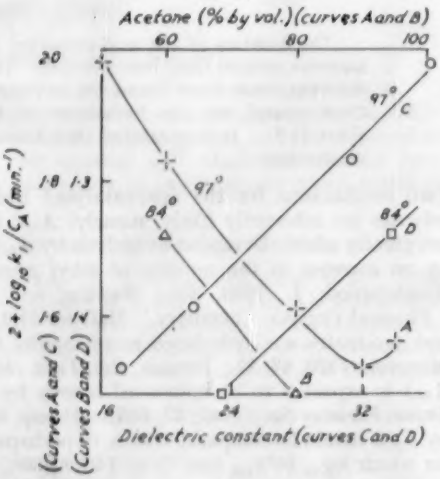


Fig. 2.



and independent of that of the ester (see Table). No significant uncatalysed reaction was detected (cf. Fig. 1, where the plot of k_1 against C_A passes through the origin). The value of $\log_{10}$ $10^6k_1/C_A$ (sec.$^{-1}$) in 60% aqueous acetone at 100° is 4·2 (calc.); this represents a rate of reaction more than 100 times that of ethyl benzoate (for which this value is 1·97), and of the ethyl esters of nine variously substituted benzoic acids studied by Timm and

Hinshelwood (*loc. cit.*). On the other hand, the rate is almost identical with that of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate, the factor being 1·17. The Arrhenius equation is accurately followed, the values of $E_{Arr.}$ being 29·2 and 30·0 kcal./mole, and $\log_{10} A_{Arr.}$ (sec.$^{-1}$) 15·3 and 15·6, in 60 and 80% acetone, respectively. These values are quite different from those found for hydrolysis by $A_{AC}2$, *viz.*, 16—20 kcal./mole and 7—8, respectively (Timm and Hinshelwood, *loc. cit.*; Newling and Hinshelwood, *J.*, 1936, 1357; Davies and Evans, *J.*, 1940, 339; Smith and Steele, *J. Amer. Chem. Soc.*, 1941, **63**, 3466), but are closely comparable with those found for *tert.*-butyl 2 : 4 : 6-trimethylbenzoate, *viz.*, 30·5 kcal./mole and 16·1, respectively (Part II), so that in the latter case their unusual magnitudes cannot be attributed to the special nature of the 2 : 4 : 6-trimethylbenzoyl portion of the ester. The variation of rate with solvent composition is similar to that found for *tert.*-butyl 2 : 4 : 6-trimethylbenzoate in aqueous acetone (Part II) and is illustrated in Fig. 2. At both 97° and 84°, $m = 0{\cdot}024$.

The microanalysis was carried out by Dr. W. Zimmermann, of C.S.I.R.O., Melbourne.

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Synthetical Experiments related to the Indole Alkaloids.

By K. T. Potts and Sir Robert Robinson.

[Reprint Order No. 6256.]

Homophthalaldehyde has been isolated and characterised. It condenses with a tryptamine salt to give (indolylethyl)*iso*quinolinium salts which, following an indication by Julian and Magnani, are reduced by lithium aluminium hydride, with spontaneous cyclisation, to bases possessing the ring-system of yohimbine.

By using two better established methods a dimethoxy compound (IX) containing the yohimbine ring-system (ring E aromatic) has been synthesised with a view to the eventual study of possible opening of ring E.

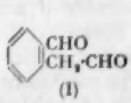
Some incidental experiments with furan derivatives are mentioned. The opening of the furan ring in various indole derivatives never led to the isolation of pure products.

In continuation of experiments on the condensation of indole derivatives with dicarbonyl compounds (cf. Robinson and Saxton, *J.*, 1953, 2596) we proposed the use of homophthalaldehyde which, combined with tryptamine, presented a number of interesting possibilities.

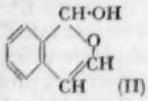
The preparation of homophthalaldehyde (Blount and Robinson, *J.*, 1933, 555) has been re-investigated since the aldehyde had never been isolated, or characterised by derivatives other than *iso*benzopyrylium ferrichloride. The dialdehyde was obtained as a colourless oil which polymerised on storage but could be regenerated by distillation.

Even a freshly distilled specimen was a mixture of the forms (I) and (II) and showed infrared bands as follows: 2·94 (associated OH), 3·52 (CH_2), 5·81 (aliphatic CHO), 5·92 (aromatic CHO), 6·24 (conjugated C:C), 8·32—8·33 μ (C:C·O·C), and 13·2 μ (*o*-disubstituted benzene).

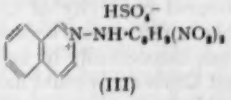
An attempt to make the 2 : 4-dinitrophenylhydrazone in the usual manner in alcoholic sulphuric acid gave 2-(2 : 4-dinitroanilino)*iso*quinolinium hydrogen sulphate (III) instead of the expected bis-2 : 4-dinitrophenylhydrazone.



(I)



(II)



(III)

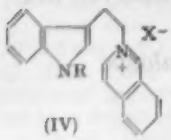
The generality of this type of reaction was established by condensation of homophthalaldehyde with methylamine, ethylenediamine, aniline, and 2-phenylethylamine to the respective *N*-substituted *iso*quinolinium salts.

With tryptamine a 2-(2-3′-indolylethyl)*iso*quinolinium salt (IV; R = H) was produced,

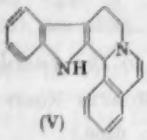
and 1-methyltryptamine gave the analogue (IV; R = Me). These salts were characterised by ultraviolet absorption spectra and by an infrared band at 6·2 μ (C:N), as well as by indole colour reactions. An alternative synthesis of (IV; R = H) was effected by condensation of 2-3′-indolylethyl bromide with *iso*quinoline in benzene (cf. Haworth and Perkin, *J.*, 1925, 1434).

In view of the reactivity of the carbinol-amine ("*iso*quinolinanol") derived from 2-methyl*iso*quinolinium salts (cf. Robinson and Robinson, *J.*, 1914, **105**, 1456) it was expected that a salt (IV; R = H) would yield the base (V) in dissociating solvents and under the influence of bases. We were at first under the impression that this cyclisation could be brought about, but the outcome of later work was ambiguous and the matter will be further investigated.

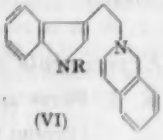
As the structure (V) does not contain the yohimbine skeleton, we have in the first place examined the possibilities of a device suggested by the work of Julian and Magnani (*J. Amer. Chem. Soc.*, 1949, **71**, 3207). Indeed these authors were led by their results to contemplate the feasibility of the process described herein and their priority in this respect is fully acknowledged. Our reading of this part of their memoir was much belated.



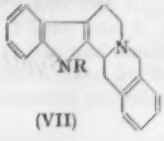
(IV)



(V)

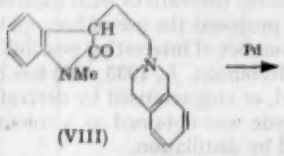


(VI)

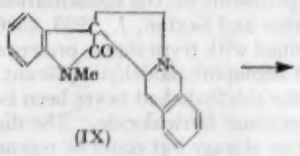


(VII)

The actual work described by Julian and Magnani concerned the reduction of an oxindole derivative by means of lithium aluminium hydride with eventual formation of the base (VII; R = Me) through the postulated intermediate (VI; R = Me). The transformation of (VI) into (VII) was considered to be spontaneous, but this is hardly likely and the reaction occurred in a solution that contained active anions and cations. Belleau recently (*Chem. and Ind.*, 1955, 229; cf. Potts, D.Phil thesis, Oxford, 1954) has made it very probable that Julian and Magnani's process was much more complex than was thought and that it proceeds in the stages shown. Dehydrogenation must also occur in the preparation of (IX) from dihydro-*N*-methylfuranoindole and tetrahydro*iso*quinoline hydrobromide, which could be generators of (VIII) (Julian, Magnani, Pikl, and Karpel, *J. Amer. Chem. Soc.*, 1948, **70**, 174). Presumably the conversion of (VIII) into (IX) proceeds



(VIII)



(IX)

(VII; R = Me)

by way of a dihydro*iso*quinoline and then by a step analogous to that taken by (VI) in its change to (VII). Thus the formation of (VII; R = Me) from (IX) involves an intramolecular rearrangement and does not necessarily go *via* (VI; R = Me), so that Julian and Magnani's prognostication that (VI) should be transformed into (VII) was based on an erroneous interpretation of their experiments. It was nevertheless perfectly correct. Belleau (*loc. cit.*) has also deduced that (VI) should yield (VII) and mentions a preliminary chromatographic observation in support.

Cationoid reactivity of $C{=}C^{*}{\cdot}NR_2$ at the atom C* is readily explicable if acids are available in the system because of the conversion into $CH{\cdot}C^{*}{=}NR_2^{+}$. However, the same effect can theoretically be achieved by complexes which can accept electrons, that is, the so-called Lewis acids could have the same effect as a proton source. The conditions under which this type of reaction occurs and the limits of its applicability require further investigation.

In the present case the reduction of the chloride (IV; R = H, X = Cl) with lithium aluminium hydride gave the base (VII; R = H), probably by way of (VI) and the related

iminium cation as explained above. The reaction also succeeded with the analogue (IV; R = Me).

The infrared and ultraviolet absorption spectra of the product (VII; R = H) were identical with those of an authentic specimen kindly provided by Professor G. R. Clemo, though the m. p. of our product was always several degrees lower than his reported m. p.; the spectra of the methyl analogue were also those characteristic of the ring system. No colour was obtained with Ehrlich's reagent. Schmid and Karrer's work (*Helv. Chim. Acta*, 1949, **32**, 960) suggests that the reduction of the *iso*quinolinium salts (IV) to dihydro-*iso*quinoline bases (VI) can be regarded as a normal event.

The tryptamine used in this and other researches in this laboratory has been synthesised for several years by what may be called the " gramine methiodide " method. In view of other reports of the synthesis of tryptamine which have appeared recently (Thesing and Schülde, *Ber.*, 1952, **85**, 324; Henbest, Jones, and Smith, *J.*, 1953, 3796) our method is reported only in so far as it differs from the others (see p. 2679). Our method of preparation of gramine methiodide gave an analytically pure specimen (cf. Geismann and Armen, *J. Amer. Chem. Soc.*, 1952, **74**, 3916) and the correlation of its properties with those reported in the literature is the subject of another communication (K. T. P.).

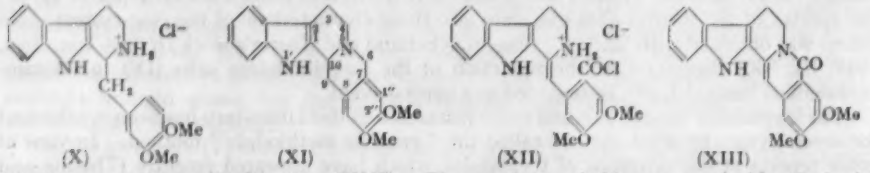
An improvement of the *iso*quinoline method of synthesis of the yohimbine ring system would be one that could employ tryptamine and a substituted *iso*quinoline instead of an indolylethyl bromide and an *iso*quinoline on the one hand, or a substituted homophthalaldehyde and tryptamine on the other.

Such a process is in course of investigation but pending the outcome of this study we have used two well-known methods for the synthesis of 3 : 4 : 6 : 9-tetrahydro-2'' : 3''-dimethoxy-7 : 8-benzoindolo(2' : 3'-1 : 2)pyridocoline (XI). The base is required as a model in attempts to imitate in the laboratory the Woodward fission of an aromatic ring E which is the characteristic step in his scheme for the biogenesis of strychnine (*Nature*, 1948, **162**, 155).

The first method was an application of that of Hahn and his collaborators (*Annalen*, 1935, **520**, 123; *Ber.*, 1938, **71**, 2193). The description given by these authors was not detailed and a supplementary account is now submitted. Tryptamine hydrochloride was condensed with 3 : 4-dimethoxyphenylpyruvic acid in aqueous solution by heating them on the boiling water-bath for several days and 1-(3 : 4-dimethoxybenzyl)-1 : 1 : 3 : 4-tetrahydro-β-carboline hydrochloride (X) was obtained directly. Ring-closure to the pentacyclic base (XI) was effected in excellent yield by refluxing with aqueous formaldehyde (cf. Swan, *J.*, 1950, 1534).

The second method is similar to that used by Späth and Lederer (*Ber.*, 1930, **63**, 120, 2102) for the synthesis of harmaline by cyclisation of the acetyl derivatives of 6-methoxytryptamine. This Bischler–Napieralski type of reaction has been much used in the indole series (Clemo and Swan, *J.*, 1946, 617; 1949, 687; Julian, Karpel, Magnani, and Meyer, *J. Amer. Chem. Soc.*, 1948, **70**, 180, 2834; Schlittler and Allemann, *Helv. Chim. Acta*, 1948, **31**, 128). 4 : 5-Dimethoxyhomophthalic anhydride was obtained in nearly quantitative yield from the corresponding acid (Perkin and Robinson, *J.*, 1907, **91**, 1081) and acetyl chloride; a poor yield was obtained when acetic anhydride was used (cf. Robinson and Young, *J.*, 1935, 1414). Tryptamine was condensed with 4 : 5-dimethoxyhomophthalic acid to give *N*-(2-3'-indolylethyl)-4 : 5-dimethoxyhomophthalimide which, after hydrolysis by alkali, gave 2-carboxy-4 : 5-dimethoxyphenyl-*N*-(2-3'-indolylethyl)acetamide (cf. Scholz, *Helv. Chim. Acta*, 1935, **18**, 923); this acid was obtained directly by the condensation of tryptamine and 4 : 5-dimethoxyhomophthalic anhydride. Esterification of the acid with diazomethane gave the methyl ester in excellent yield and, when this ester was heated under reflux with phosphoryl chloride, alone or in toluene, a compound which appears to be 1-(2-chlorocarbonyl-4 : 5-dimethoxybenzylidene)-1 : 2 : 3 : 4-tetrahydro-β-carboline hydrochloride (XII) was obtained. The same substance was formed when 2-carboxy-*N*-(2-3'-indolylethyl)-4 : 5-dimethoxyphenylacetamide was treated with phosphoryl chloride. It separated from methanol as orange needles and had the composition, $C_{21}H_{20}N_2O_2Cl_2$; ionic chlorine was found to be present and the absence of a free α-position in the indole nucleus was shown by its failure to give a colour with Ehrlich's reagent or with vanillin

and hydrochloric acid. Its solutions in organic solvents had a greenish fluorescence and its ultraviolet absorption was consistent with extensive conjugation in the molecule (max. at 4300 Å). The infrared spectrum showed bands at 3·03 (>NH), 6·15 (C:C), 6·23 (benzene ring), and 6·25 μ (conjugated ·COCl). Treatment of this salt (XII) with sodium hydroxide



(X) (XI) (XII) (XIII)

solution gave the cyclised lactam (XIII). The spectrum of this was nearly identical with that of 3 : 4-dihydro-6-oxo-7 : 8-benzoindolo(2′ : 3′-1 : 2)pyridocoline prepared by Clemo and Swan (*loc. cit.*). An infrared band at 6·3 μ can be attributed to the cyclic amide group. This appears to be one of the few instances in which the intermediate product in such a cyclisation has been isolated. The product soon crystallised from the reaction mixture and it is probable that this separation prevented the reaction from proceeding to completion. It is conceivable that the red, crystalline material obtained by Clemo and Swan (*loc. cit.*) on treatment of *N*-(2-3′-indolylethyl)homophthalimide with phosphoryl chloride in toluene may have a similar structure.

On reduction with lithium aluminium hydride in tetrahydrofuran solution (cf. Ehrlich, *J. Amer. Chem. Soc.*, 1948, **70**, 2286; Clemo *et al.*, *Nature*, 1948, **162**, 296) the lactam (XIII) gave an excellent yield of the dihydrobenzoindolopyridocoline (XI with a 9 : 10-double bond). The ultraviolet absorption spectrum of this compound showed a small change to longer wavelength after the material had been in solution for several hours, probably owing to migration of the 9 : 10-double bond. Hydrogenation in the presence of Adams catalyst in acetic acid at room temperature and pressure gave the tetrahydro-compound (XI), identical with the specimen prepared by the first method.

The use to be made of the base (XI) depends on the outcome of experiments with simpler substances and, of these, 2 : 3-dihydroxynaphthalene, 6 : 7-dihydroxytetralin, and 1 : 2 : 3 : 4-tetrahydro-6 : 7-dihydroxy*iso*quinoline, and their methyl ethers are the preferred models.

The opportunity is now taken to describe some experiments with furan derivatives, the ring-fission of which might produce reactive groupings that could facilitate syntheses in the indole group. In general this approach has been disappointing, especially with pendent furyl residues in indole derivatives. The desired substances can naturally be synthesised but are either unchanged by acid reagents or, if reactive, are converted into intractable materials. The Experimental section should be consulted for details but attention may be drawn to the fact that, although the product of the bromination of furfuraldehyde diacetate in methanol, namely, 2 : 5-dimethoxy-2 : 5-dihydrofurfuraldehyde diacetate, has been obtained as a crystalline solid, about 25% of the product remained as an oil and this may contain stereoisomerides. No smooth ring-fission of any one of the 2-furyl derivatives described could be realised.

Experimental

Ultraviolet absorption spectra are for MeOH solutions.

Homophthalaldehyde (I ⇌ II).—*trans*-Indane-1 : 2-diol (4·5 g.) (Porter and Suter, *J. Amer. Chem. Soc.*, 1935, **57**, 2023) in dry benzene (100 c.c.) was gradually treated with lead tetra-acetate (13·4 g.) during 5 min., the solution being kept just boiling and occasionally shaken. After boiling for a few minutes the mixture was cooled and filtered, and the clear solution concentrated to a small volume under reduced pressure on the steam-bath. Ether (*ca.* 150 c.c.) was added and the solution shaken with saturated sodium hydrogen carbonate solution, washed with water, and dried (Na_2SO_4). The *aldehyde* was obtained as a mobile oil with an aromatic, benzaldehyde-like odour (2·7 g., 60%), b. p. 93°/0·4 mm., n_D^{18} 1·5680 (Found : C, 72·9; H, 5·6%; *M*, 196. $C_9H_8O_2$ requires C, 72·9; H, 5·4%; *M*, 148). Light absorption : $\lambda_{max.}$ 2600 (log ε 3·03), $\lambda_{inflex.}$ 2875 (log ε 2·22), $\lambda_{min.}$ 2300 Å (log ε 2·38). The aldehyde reduced an ammoniacal

silver solution and gave a positive Schiff reaction after a few minutes. When it was heated on the steam-bath with aqueous ammonia, *iso*quinoline was quickly produced [picrate (from water), m. p. and mixed m. p. 225°].

The aldehyde is oxidised to phthalic acid by acid permanganate on the steam-bath.

A solution of potassium borohydride (1·1 g.) in water (20 c.c.) was added, slowly and with shaking, to one of homophthalaldehyde (2·8 g.) in 75% ethanol (15 c.c.). The solution immediately became orange-coloured, and straw-yellow on addition of further quantities of the reagent. After 30 minutes' refluxing, excess of the hydride was decomposed by dilute sulphuric acid. The solution was continuously extracted with ether for 8 hr. and, after drying (Na_2SO_4) and evaporation of the ether extract, 2-2′-hydroxyethylbenzyl alcohol was obtained as a colourless oil, b. p. 130°/0·5 mm. (Anderson and Holliman, *J.*, 1950, 1037, report b. p. 194—196°/15 mm.). The diphenylurethane, white needles from benzene, had m. p. 133—134° (*idem*, *loc. cit.*, give m. p. 133—133·5°).

With alcoholic 2 : 4-dinitrophenylhydrazine containing a small amount of sulphuric acid the aldehyde gave a light orange, crystalline precipitate which, recrystallised from ethanol (charcoal), afforded 2-(2 : 4-*dinitroanilino*)*iso*quinolinium *hydrogen sulphate* (III) as pale cream needles, m. p. 235° (Found : C, 44·2, 44·2; H, 3·2, 3·1; N, 13·7, 13·7. $C_{15}H_{12}O_8N_4S$ requires C, 44·1; H, 3·0; N, 13·7%). Light absorption : $\lambda_{max.}$ 2300, 3050, 3250 (log ε 4·59, 4·14, 41·5); $\lambda_{min.}$ 2800, 3150 Å (log ε 4·96, 4·12).

3-2′-*Dimethylaminoethylindole Methiodide* (*Gramine Methiodide*).—A solution of gramine (130 g.; Kuhn and Stein, *Ber.*, 1937, **70**, 567) in absolute alcohol (1 l.) was cooled to 0° and methyl iodide (104 c.c.) added during an hour with stirring at about 0°. Dry ether was added until a slight cloudiness appeared and the mixture then kept overnight in the refrigerator. The crystalline *methiodide* (223 g., 94%) which had separated was collected and dried in a vacuum-desiccator. It had m. p. 162—163° (Found : C, 45·9, 45·6; H, 5·7, 5·4; N, 9·3, 8·5. $C_{12}H_{17}N_2I$ requires C, 45·6; H, 5·4; N, 8·9%). Light absorption : $\lambda_{max.}$ 2700, 2800 (log ε 3·61, 3·61), $\lambda_{min.}$ 2450, 2750 Å (log ε 3·25, 3·59).

3-*Indolylacetonitrile*.—A solution of recrystallised sodium cyanide (100 g.) in water (2 l.) was heated to incipient boiling and gramine methiodide (220 g.) added as quickly as possible. The mixture was heated on a vigorously boiling water-bath for 25 min., with stirring. After cooling, the oil which had separated was isolated by means of chloroform. During this operation some 3-indolylacetamide, m. p. 149—150° (Baker and Happold, *Biochem. J.*, 1940, **34**, 657, record m. p. 150—151°) separated and was removed. The pale yellow, viscous oil was distilled as rapidly as possible using a short-path still and 3-indolylacetonitrile (67·4 g., 70%) was obtained as a nearly colourless, viscous oil, b. p. 159—160°/0·2 mm. Majima and Hoshino (*Ber.*, 1925, **58**, 2042) record b. p. 160°/0·2 mm. The nitrile crystallised in an ice–salt mixture but was always partly liquid at room temperature (Henbest, Jones, and Smith, *J.*, 1953, 3796, record m. p. 36—36·5°). The picrate separated from alcohol as orange needles, m. p. 128° (Majima and Hoshino, *loc. cit.*, give m. p. 127—128°).

3-*Indolylacetic Acid*.—3-Indolylacetamide (2 g.) was hydrolysed with an excess of boiling 8% sodium hydroxide solution (2—3 hr.). The acid crystallised from water as almost colourless plates, m. p. 165°, alone or mixed with an authentic specimen (Found : C, 68·2; H, 5·1. Calc. for $C_{10}H_9O_2N$: C, 68·6; H, 5·2%). The picrate was obtained as clusters of brick-red needles, m. p. 178°. Majima and Hoshino, *loc. cit.*, record m. p. 164·5—165° for the acid and 178° for the picrate.

Condensation of Tryptamine with Homophthalaldehyde.—Solutions of tryptamine (4·8 g.) in acetic acid (30 c.c.) and of homophthalaldehyde (4·4 g.) in acetic acid (10 c.c.) were mixed and then heated on the steam-bath for 4 hr., the orange yellow colour gradually deepening. The solvent was removed under reduced pressure on the steam-bath, and portions of the oily residual 2-(2-3′-indolylethyl)*iso*quinoline treated with a slight excess of the appropriate acid affording the following salts (IV; R = H) : *picrate* (from methanol; charcoal), bronze plates, m. p. 208° (Found : C, 59·7; H, 4·0; N, 14·1. $C_{25}H_{19}O_7N_5$ requires C, 59·9; H, 3·8; N, 14·0%); *perchlorate* (from methanol; charcoal), lemon-coloured blades, m. p. 223° (Found : C, 61·5; H, 4·3; N, 7·5; Cl, 9·5. $C_{19}H_{17}O_4N_2Cl$ requires C, 61·2; H, 4·6; N, 7·5; Cl, 9·5%); *iodide*, canary-yellow needles (from methanol; charcoal), m. p. 245° (Found : C, 56·6; H, 4·3; N, 6·9; I, 31·6. $C_{19}H_{17}N_2I$ requires C, 57·0; H, 4·3; N, 7·0; I, 31·7%) [light absorption : $\lambda_{max.}$ 2250, 2800, 3400 (log ε 4·62, 3·98, 3·75), $\lambda_{min.}$ 2500, 3100 Å (log ε 3·72, 3·51)]; *chloride* (from wet acetone; charcoal), yellow needles, m. p. 128° (Found : C, 70·2, 69·9; H, 5·9, 6·3; N, 8·4. $C_{19}H_{17}N_2Cl,H_2O$ requires C, 69·8; H, 5·9; N, 8·6%).

In a run in which tryptamine (1·3 g.) in acetic acid (10 c.c.) and homophthalaldehyde (1·3 g.)

in acetic acid (10 c.c.) were condensed together on the steam-bath for 4 hr. and the product isolated as the chloride, the yield was 2·2 g. (88%), m. p. 122°, raised to 128° on crystallisation.

Condensation of 1-*Methyltryptamine with Homophthalaldehyde.*—A mixture of 1-methyltryptamine (1·7 g.) (prepared by the method of Potts and Saxton, *J.*, **1954**, 2641) and homophthalaldehyde (1·5 g.) in acetic acid (20 c.c.) was heated on the steam-bath for 1 hr. The condensation product was again converted into a series of salts of (IV; R = Me), all crystallising from methanol (charcoal): 2-(2-1′-*Methyl*-3′-*indolylethyl*)*iso*quinolinium *iodide*, golden needles, m. p. 229° (Found: C, 58·1; H, 4·7; N, 6·4. $C_{20}H_{19}N_2I$ requires C, 58·0; H, 4·6; N, 6·8%); *picrate*, pale yellow nodules, m. p. 234° (Found: C, 60·8; H, 4·4; N, 14·0. $C_{26}H_{21}O_7N_5$ requires C, 60·6; H, 4·1; N, 13·6%); *perchlorate*, lemon-yellow plates, m. p. 191° (Found: C, 62·0; H, 5·1; N, 7·6. $C_{20}H_{19}O_4N_2Cl$ requires C, 62·1; H, 5·0; N, 7·2%); *chloride*, yellow, hygroscopic needles, m. p. 192° (Found: C, 67·4; H, 7·0. $C_{20}H_{19}N_2Cl,2·5CH_3·OH$ requires C, 67·1; H, 7·2%).

Condensation of 2-3′-*Indolylethyl Bromide and* iso*Quinoline.*—A mixture of 2-3′-indolylethyl bromide (0·5 g.; Hoshino and Shimodaira, *Annalen*, 1935, **520**, 25), *iso*quinoline (0·3 g.), and dry benzene (9 c.c.) was kept for 24 hr. and then evaporated under reduced pressure on the steam-bath. A concentrated solution of potassium iodide was added to the gummy residue, and the supernatant liquid decanted from the oil which separated. When rubbed with acetone, the product crystallised as yellow needles, m. p. 244°. Recrystallisation from methanol (charcoal) raised the m. p. to 245°, alone or mixed with 2-(2-3′-indolylethyl)*iso*quinolinium iodide prepared as above using homophthalaldehyde. An alcoholic solution of the iodide, treated with alcoholic picric acid, gave a picrate which crystallised from methanol as orange columns, m. p. and mixed m. p. 207°. The corresponding perchlorate crystallised from methanol as lemon-yellow blades, m. p. and mixed m. p. 223°. When acetic acid was used as the medium for the condensation, the product was obtained in an impure state in lower yield.

Condensation of 2-3′-*Indolylethyl Bromide and* 6 : 7-*Dimethoxy*iso*quinoline.*—Solutions of 2-3′-indolylethyl bromide (0·9 g.) in benzene (7 c.c.) and of 6 : 7-dimethoxy*iso*quinoline (0·8 g.) in benzene (5 c.c.) were mixed and kept at room temperature for several weeks, the bromide (0·5 g., 32%, m. p. 197°) gradually crystallising. 2-(2-3′-*Indolylethyl*)-6 : 7-*dimethoxy*iso*quinolinium bromide* crystallised from methanol–ether (charcoal) as irregular, fawn-coloured prisms, m. p. 219° (decomp.) (Found: C, 60·1, 60·2; H, 5·3, 5·5. $C_{21}H_{21}O_2N_2Br,0·5CH_3·OH$ requires C, 60·1; H, 5·4%), which with aqueous potassium iodide gave the *iodide* which crystallised from water (charcoal) as irregular prisms, m. p. 246—247° (decomp.) (Found: C, 54·5; H, 4·8; N, 6·4. $C_{21}H_{21}O_2N_2I$ requires C, 54·8; H, 4·6; N, 6·1%). Attempted reduction of this salt by lithium aluminium hydride did not succeed but we have reason to believe that it might work with the chloride. The corresponding *picrate* crystallised from methanol (charcoal) as brown blades, m. p. 180° (Found: C, 50·6, 50·2; H, 3·6, 3·7; N, 14·4, 13·8. $C_{33}H_{26}O_{16}N_8$ requires C, 50·2; H, 3·3; N, 14·2%).

Condensation of 2-*Phenylethylamine with Homophthalaldehyde.*—A solution of 2-phenylethylamine (1·0 g.) and homophthalaldehyde (1·2 g.) in acetic acid (20 c.c.) was heated on the steam-bath for 2 hr. 2-2′-Phenylethyl*iso*quinolinium salts were obtained from the product as follows: *picrate* (from methanol), yellow, hexagonal rods, m. p. 160° (Found: C, 59·5; H, 3·8. $C_{23}H_{16}O_7N_4$ requires C, 59·7; H, 3·9%); *perchlorate* (from methanol; charcoal), colourless, rectangular rods, m. p. 167° (Found: C, 61·6; H, 4·9. $C_{17}H_{16}O_4NCl$ requires C, 61·2; H, 4·8%); *iodide*, pale yellow, irregular prisms, m. p. 179° (from acetone–ether; charcoal) (Found: C, 56·8; H, 4·7. $C_{17}H_{16}NI$ requires C, 56·5; H, 4·5%) [light absorption: $\lambda_{max.}$ 2300, 2700, 2800, 3350 (log ε 4·58, 3·60, 3·59, 3·60), $\lambda_{min.}$ 2550, 3000 Å (log ε 3·56, 3·12)].

Condensation of Aniline with Homophthalaldehyde.—Aniline (0·9 g.) was added to homophthalaldehyde (1·4 g.) in acetic acid (10 c.c.). The solution became orange-yellow and was heated on the steam-bath for 5 min., then excess of acetic acid was removed under reduced pressure and alcoholic picric acid added to the oily residue. An immediate crystalline precipitate of 2-phenyl*iso*quinolinium picrate was obtained which crystallised from methanol as yellow needles, m. p. 126° (Schöpf, Hartmann, and Koch, *Ber.*, 1936, **69**, 2768, report m. p. 125—127°) (Found: C, 57·8; H, 3·6. Calc. for $C_{21}H_{14}O_7N_4$: C, 58·1; H, 3·3%). The condensation was also effected without use of any solvent but with no advantage.

Condensation of Ethylenediamine with Homophthaldehyde.—Solutions of aqueous ethylenediamine (0·9 g. of 70%) in acetic acid (5 c.c.) and of homophthalaldehyde (2·5 g.) in acetic acid (10 c.c.) were mixed and heated on the steam-bath for 30 min. The condensation product was characterised as in previous cases by formation of the following derivatives:

Ethylenebis-2-iso*quinolinium dipicrate* (from a large volume of glacial acetic acid), yellow

needles, m. p. 264° (decomp.) (Found : C, 52·2; H, 3·1; N, 15·4. $C_{32}H_{28}O_{14}N_8$ requires C, 51·8; H, 3·0; N, 15·1%); *diperchlorate* (from water; charcoal), white, hexagonal plates, m. p. 296° (decomp.) (Found : C, 49·4; H, 3·7; N, 5·7. $C_{30}H_{18}O_8N_8Cl_2$ requires C, 49·5; H, 3·7; N, 5·8%); *di-iodide* (from water; charcoal), orange cubes, m. p. 287° (decomp.) (Found : C, 44·7; H, 3·6; N, 5·2. $C_{29}H_{18}N_2I_2$ requires C, 44·5; H, 3·4; N, 5·2%) [light absorption : $\lambda_{max.}$ 2400, 2800, 3400 (log ε 4·66, 3·91, 3·94), $\lambda_{min.}$ 2650, 3000 Å (log ε 3·85, 3·53)]; *dichloride* (from methanol–ether), white, irregular prisms, m. p. 282° (decomp.) (Found : C, 61·2, 61·2; H, 5·6, 5·6. $C_{29}H_{18}N_2Cl_2,2H_2O$ requires C, 61·1; H, 5·6%).

Condensation of Methylamine with Homophthalaldehyde.—A solution of methylamine (1·5 g. of 20% aqueous solution) in acetic acid (15 c.c.) was mixed with one of homophthalaldehyde (1·3 g.) in acetic acid (10 c.c.) and heated on the steam-bath for 30 min. 2-*Methylisoquinolinium picrate* was obtained as needles (from methanol), m. p. 170° (Found : C, 51·9; H, 3·5; N, 14·9. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·3; N, 15·1%). The *perchlorate* (from water), formed irregular prisms, m. p. 177° (Found : C, 49·5; H, 4·0; N, 5·4. $C_{10}H_{10}O_4NCl$ requires C, 49·3; H, 4·1; N, 5·8%).

3 : 4 : 6 : 9-*Tetrahydro*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (VII; R = H).—Finely powdered 2-(2-3′-indolylethyl)*iso*quinolinium chloride (1 g.) was added in small portions during 5 min. to a suspension of lithium aluminium hydride (0·5 g.) in ether (100 c.c.). After 2 hr. at the room temperature the excess of the hydride was decomposed by careful addition of water. On addition of dilute hydrochloric acid a gum separated which solidified in contact with methanol. The *hydrochloride* crystallised from methanol (charcoal) as colourless columns, m. p. 208—209° (decomp.) (Found : C, 73·5; H, 6·3; N, 8·8. $C_{19}H_{19}N_2Cl$ requires C, 73·4; H, 6·2; N, 9·0%). Light absorption : $\lambda_{max.}$ 2250, 2700, 2890 (log ε 4·54, 4·00, 3·86), $\lambda_{min.}$ 2400, 2850 Å (log ε 3·54, 3·85). The colourless solution in 80% sulphuric acid became light green on the addition of ferric chloride. The free base crystallised from methanol (charcoal) as white needles, m. p. 188—189° (decomp.) with darkening and previous sintering (Clemo and Swan, *J.*, 1946, 617, report m. p. 196—197°) (Found : C, 83·0; H, 6·6; N, 10·1. Calc. for $C_{19}H_{18}N_2$: C, 83·2; H, 6·6; N, 10·2%). Light absorption : $\lambda_{max.}$ 2800 (log ε 4·3), $\lambda_{min.}$ 2480 Å (log ε 3·64). The *picrate* crystallised from aqueous acetone as pale yellow needles, m. p. 173° with previous sintering (*idem*, *loc. cit.*, gave m. p. 173—174°) (Found : C, 59·5; H, 4·3; N, 14·4. $C_{25}H_{21}O_7N_5$ requires C, 59·6; H, 4·2; N, 13·9%). The *methiodide*, prepared in hot acetone, crystallised from methanol–ether as white, irregular prisms, m. p. 178—179° (Found : C, 57·9, 57·5; H, 5·9, 5·8; N, 6·6. $C_{20}H_{21}N_2I,0·5C_3H_6O$ requires C, 57·9; H, 5·4; N, 6·3%). Confirmation of the presence of acetone of crystallisation was obtained by means of the sodium nitroprusside–alkali and the *m*-dinitrobenzene–alkali colour reaction.

3 : 4 : 6 : 9-*Tetrahydro*-1′-*methyl*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (VII; R = Me).—2-(2-1′-Methyl-3′-indolylethyl)*iso*quinolinium chloride (1·0 g.) was added to a suspension of lithium aluminium hydride (0·5 g.) in ether (150 c.c.). After 2 hr. at the room temperature, most of the ether was removed and the excess of lithium aluminium hydride decomposed by the addition of water and dilute hydrochloric acid. The gum which separated was collected and dissolved in water; addition of sodium hydroxide solution gave the required base which was isolated by means of ether as an oil which did not crystallise. It distilled at 170—180° (bath)/0·01 mm. (Julian and Magnani, *loc. cit.*, report m. p. 135°) (Found : C, 82·5; H, 7·4; N, 9·8. Calc. for $C_{20}H_{20}N_2$: C, 83·2; H, 7·0; N, 9·7%). Light absorption : $\lambda_{max.}$ 2250, 2900 (log ε 4·42, 3·76), $\lambda_{min.}$ 2550 Å (log ε 3·46). The main absorption bands in the infrared spectrum occur at 3·45, 6·16, 6·64, 7·30, and 13·45—13·6 μ. The picrate separated from methanol as small, reddish yellow needles, m. p. 208—209° (decomp.) [*idem*, *loc. cit.*, give m. p. 209° (decomp.)].

Reduction of 2-(2-3′-*Indolylethyl*)*isoquinolinium Chloride with Potassium Borohydride.*—This chloride (0·5 g.) in water (10 c.c.) was treated with a solution of potassium borohydride (0·2 g.) in 50% methanol (6 c.c.). The solution was refluxed for 10 min. and then the excess of hydride was decomposed by dilute hydrochloric acid. The solution was concentrated and the gum which was obtained afforded a small amount of 3 : 4 : 6 : 9-tetrahydro-7 : 8-benzoindolo(2′ : 3′-1 : 2)pyridocoline hydrochloride, m. p. 287—288° (decomp.) alone or mixed with the salt reported above.

1 : 2 : 3 : 4-*Tetrahydro*-2-(2-3′-*indolylethyl*)*isoquinoline.*—*N*-(2-3′-Indolylethyl)homophthalimide (200 mg.; Clemo and Swan, *J.*, 1946, 617) was added to a solution of lithium aluminium hydride (100 mg.) in ether (50 c.c.) and the mixture was refluxed for 3 hr. with stirring under nitrogen. The excess of lithium aluminium hydride was decomposed with water, dilute hydrochloric acid added, and the ethereal layer separated. Unchanged imide was recovered from this ether solution. The aqueous layer was basified and a small amount of an

oil extracted with ether. This afforded an orange *picrate*, m. p. *ca.* 135°. It crystallised from aqueous acetone as orange, fern-like aggregates, m. p. 171° (Found : C, 59·6; H, 4·6. $C_{25}H_{25}O_7N_5$ requires C, 59·4; H, 4·6%). The infrared spectrum showed no band in the carbonyl region. Ring-closure during the reduction is excluded since the substance shows a strong Ehrlich reaction, a reddish-purple coloration.

1-(3 : 4-*Dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline Hydrochloride* (X).—A solution of tryptamine hydrochloride (3·4 g.) in water (50 c.c.) was mixed with 3 : 4-dimethoxyphenylpyruvic acid (3·9 g.; *Org. Synth.*, Coll. Vol. II, pp. 55, 335) dissolved in a mixture of warm ethanol (40 c.c.) and water (400 c.c.), and the red solution was then heated on the steam-bath for 72 hr. The solution was evaporated to dryness under reduced pressure, the residue dissolved in hot methanol (charcoal), the solution concentrated, and the hydrochloride (X) (3·7 g., 66%; m. p. 234—235°) precipitated by ether. It crystallised from methanol–ether as needles, m. p. 236° (Hahn, Schales, Bärwald, and Werner, *Annalen*, 1935, **520**, 109, reported m. p. 230°) (Found : C, 66·6; H, 6·5; N, 7·4. Calc. for $C_{20}H_{23}O_2N_2Cl$: C, 66·9; H, 6·5; N, 7·8%). The base obtained from this salt crystallised from ether–light petroleum as needles, m. p. 91°, or from water as long, white needles, m. p. 98° (Hahn and Hansel, *Ber.*, 1938, **71**, 2192, report m. p. 98°). An alcoholic solution of the tetrahydro-β-carboline showed a pale blue fluorescence in ultraviolet light, quenched by the addition of acid. The addition of ferric chloride to the colourless solution in 80% sulphuric acid gave a dull green colour which was moderately stable. With chromic acid it gave a transient purple colour which quickly became green. Light absorption : $\lambda_{max.}$ 2250, 2800 (log ε 4·49, 4·04), $\lambda_{min.}$ 2450 Å (log ε 3·52).

3 : 4 : 6 : 9-*Tetrahydro*-2″ : 3″-*dimethoxy*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (XI).—The above β-carboline hydrochloride (2·9 g.), 40% aqueous formaldehyde (60 c.c.), and water (400 c.c.) were refluxed together for 6 hr. (a) *Isolation as the hydrochloride.* The solution was evaporated to dryness under reduced pressure and the residue dissolved in boiling methanol, the solution decolorised (charcoal), and the hydrochloride, m. p. 263°, precipitated by the addition of ether. It crystallised from methanol–ether as white plates, m. p. 276°, and decomposed just above the m. p. (*idem, loc. cit.*, give m. p. 254—255° after sintering at 250°) (Found : C, 68·3; H, 6·3; N, 6·8; Cl, 10·3. Calc. for $C_{21}H_{23}O_2N_2Cl$: C, 68·0; H, 6·3; N, 7·5; Cl, 9·6%). (b) *Isolation as the base.* The concentrated solution was made alkaline with sodium hydroxide, and the precipitated product (2·6 g., *ca.* 90%; m. p. 285°) collected and washed well with water. The base crystallised from aqueous acetone as fern-like aggregates of colourless needles, m. p. 294—295° (*idem, loc. cit.*, give m. p. 249—250°) (Found : C, 75·3; H, 6·5; N, 8·4. Calc. for $C_{21}H_{22}O_2N_2$: C, 75·4; H, 6·6; N, 8·4%). Light absorption : $\lambda_{max.}$ 2250, 2800 (log ε 4·48, 4·08), $\lambda_{min.}$ 2500 Å (log ε 3·69). The picrate crystallised from aqueous acetone as yellow needles, darkening at 175° and decomposing at about 180° (*idem, loc. cit.*, give m. p. 173—174°) (Found : C, 57·8; H, 5·1. Calc. for $C_{27}H_{25}O_9N_5,0{\cdot}5C_3H_6O$: C, 57·8; H, 4·8%).

4 : 5-*Dimethoxyhomophthalic Anhydride.*—4 : 5-Dimethoxyhomophthalic acid (5·0 g.) and acetyl chloride (35 c.c.) were refluxed together for 2 hr. All the acid had gone into solution after 90 min. and 4 : 5-*dimethoxyhomophthalic anhydride* crystallised on cooling. The excess of acetyl chloride and acetic acid was removed by evaporation and the anhydride crystallised from benzene (charcoal) as felted, cream needles (4·6 g.), m. p. 175°. It retained traces of solvent very tenaciously and was sublimed at *ca.* 170—180° (bath)/0·03 mm. and so obtained as white needles, m. p. 175° (Found : C, 60·0; H, 4·6. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

N-(2-3′-*Indolylethyl*)4 : 5-*dimethoxyhomophthalimide.*—An intimate mixture of tryptamine (1·6 g.) and 4 : 5-dimethoxyhomophthalic acid (2·4 g.) was heated at 180° for 2 hr.; the dark brown melt was then extracted with hot methanol (charcoal). The *imide* (2·9 g., 81%) crystallised from methanol as light brown needles, m. p. 195°, and, after sublimation at 180—200° (bath)/0·01 mm. and crystallisation from methanol, it was obtained as pale cream needles, m. p. 199° (Found : C, 69·3; H, 5·6. $C_{21}H_{20}O_4N_2$ requires C, 69·2; H, 5·5%). It gave a yellow solution in concentrated sulphuric acid and an orange-red solution in concentrated nitric acid. Its alkaline solution had a brilliant green fluorescence in ultraviolet light. With Ehrlich's reagent it gave a red colour on heating; the colour disappeared on cooling; this colour change could be repeated indefinitely.

2-*Carboxy*-4 : 5-*dimethoxyphenyl*-N-(2-3′-*indolylethyl*)*acetamide.*—(a) *From* 4 : 5-*dimethoxyhomophthalic anhydride.* A solution of tryptamine (1·6 g.) and 4 : 5-dimethoxyhomophthalic anhydride (2·2 g.) in benzene (75 c.c.) was refluxed for 9 hr. Crystals, together with some oil, separated after 30 min.; after cooling, all the separated material crystallised. 2-*Carboxy*-4 : 5-*dimethoxyphenyl*-N-(2-3′-*indolyethyl*)*acetamide* (3·7 g., 96%; m. p. 185°) crystallised from

methanol as white cubes, m. p. 185·5° (Found : C, 65·9; H, 5·9; N, 7·4. $C_{21}H_{22}O_5N_2$ requires C, 65·9; H, 5·8; N, 7·3%). It was soluble in the common organic solvents, and in concentrated sulphuric acid it developed an orange-red colour changing to yellow and then reddish-brown on warming; with concentrated nitric acid it gave a yellow solution. A positive Ehrlich test was obtained on warming; the colour disappeared on cooling. When chloroform was used as the solvent in the condensation the yield was 76%. Light absorption : $\lambda_{max.}$ 2250, 2650 (log ε 4·64, 4·06), $\lambda_{min.}$ 2400 Å (log ε 3·75).

(b) *By the hydrolysis of* N-(2-3′-*indolylethyl*)-4 : 5-*dimethoxyhomophthalimide*. A solution of the imide (1·3 g.) in 2N-sodium hydroxide (25 c.c.) was heated on the steam-bath for 12 hr. The hot alkaline solution was decolorised with charcoal, cooled, and acidified with concentrated hydrochloric acid, and the flocculent, fawn precipitate (1·1 g., 80%) collected. After several crystallisations from methanol it separated as white cubes, m. p. 184—185°, alone or mixed with a specimen prepared by method (a).

N-(2-3′-*Indolylethyl*)-2-*methoxycarbonyl*-4 : 5-*dimethoxyphenylacetamide*.—The foregoing acid (0·38 g.) and an excess of ethereal diazomethane containing a little methanol were left for 2 hr. at room temperature, the solvent was removed, the residue dissolved in methanol, and the solution filtered from a small amount of solid. The addition of water to the concentrated solution precipitated the *ester* (0·36 g., 90%) which crystallised from aqueous methanol (charcoal) as cream needles, m. p. 170° (Found : C, 66·8; H, 6·3; N, 7·0. $C_{22}H_{24}O_5N_2$ requires C, 66·7; H, 6·1; N, 7·1%). With Ehrlich's reagent it gave a red colour on heating, and on cooling the colour faded.

1-(2-*Chlorocarbonyl*-4 : 5-*dimethoxybenzylidene*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline Hydrochloride* (XII).—A mixture of the above ester (0·4 g.), phosphoryl chloride (5 c.c.), and toluene (5 c.c.) was refluxed for 2 hr. After 90 min., orange yellow crystals separated and these were collected (0·34 g., 84%; m. p. 271°) after cooling. A further, small quantity of material was obtained from the mother-liquor by evaporation to dryness and extraction of the residue with chloroform. The *hydrochloride* crystallised from methanol (charcoal) as orange needles, m. p. 273° (Found : C, 60·0, 60·1; H, 5·0, 4·7; N, 6·6; Cl, 17·4. $C_{21}H_{20}O_3N_2Cl_2$ requires C, 60·2; H, 4·8; N, 6·7; Cl, 16·9%). Its solution in organic solvents exhibited a light green fluorescence in ultraviolet light and the yellow solution in concentrated sulphuric acid also had a green fluorescence. No colour was obtained with Ehrlich's reagent or with vanillin and hydrochloric acid. Light absorption : $\lambda_{max.}$ 2350, 2650, 3200, 3600, 4300 (log ε 4·28, 4·57, 4·78, 4·57, 3·93), $\lambda_{min.}$ 2300, 2450, 2850, 3400, 4000 Å (log ε 4·27, 4·26, 4·13, 4·53, 3·79).

3 : 4-*Dihydro*-2″ : 3″-*dimethoxy*-6-*oxo*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (XIII).—The above acid chloride hydrochloride (100 mg.), dissolved in water (50 c.c.) containing a little alcohol, was treated with 10% sodium hydroxide solution (*ca.* 5 c.c.). The colour of the solution immediately disappeared and a product separated. The mixture was gently heated on the steam-bath for 5 min., then cooled, and the solid collected (85 mg.; m. p. 288°). The *lactam* crystallised from aqueous methanol (charcoal) as lemon-yellow needles, m. p. 292° (Found : C, 73·2; H, 5·6; N, 7·6. $C_{21}H_{18}O_3N_2$ requires C, 72·8; H, 5·2; N, 8·1%). Its colourless solution in methanol showed a blue fluorescence which was intensified in ultraviolet light. With concentrated sulphuric acid it gave a bright yellow solution, with concentrated nitric acid a dull orange-red colour, and with chromic acid it gave a transient yellow green changing to dull red in a few minutes. It was insoluble in hot concentrated hydrochloric acid and in hot sodium hydroxide solution. Light absorption : $\lambda_{max.}$ 2300, 2550, 3450, 3650, 3800 (log ε 4·73, 4·70, 4·62, 4·63, 4·54), $\lambda_{min.}$ 2250, 2400, 2950, 3550, 3750 Å (log ε 4·52, 4·54, 3·87, 4·57, 4·47).

3 : 4-*Dihydro*-2″ : 3″-*dimethoxy*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (as XI, but $\Delta^{9(10)}$).—The above, pure lactam (260 mg.) in tetrahydrofuran (30 c.c.) was added to a slurry of lithium aluminium hydride (200 mg.) in ether (10 c.c.), and the yellow solution refluxed for 3 hr. with stirring under nitrogen. Excess of the hydride was decomposed with water, the solution acidified with hydrochloric acid, and the tetrahydrofuran distilled from the steam-bath under reduced pressure. The mother-liquor, after cooling, deposited fine, canary-yellow needles (250 mg., 90%), m. p. 230° with frothing. 3 : 4-*Dihydro*-2″ : 3″-*dimethoxy*-7 : 8-*benzoindolo*-(2′ : 3′-1 : 2)*pyridocoline hydrochloride* crystallised from water as brilliant, yellow needles, m. p. *ca.* 240—245° with frothing (Found : C, 62·8; H, 5·9; N, 6·9; Cl, 8·9. $C_{21}H_{21}O_3N_2Cl,2H_2O$ requires C, 62·3; H, 6·2; N, 6·9; Cl, 8·8%). Light absorption : $\lambda_{max.}$ 2650, 3200, 3600 (log ε 5·47, 5·58, 5·56), $\lambda_{min.}$ 2400, 2800, 3350 Å (log ε 5·16, 5·08, 5·44). A solution of the hydrochloride (200 mg.) in water was made alkaline with sodium hydroxide solution, and the precipitated *base* [150 mg.; m. p. 224—225° (decomp.)] collected. It crystallised from aqueous acetone as irregular, bright yellow prisms, decomposing at *ca.* 227° with previous shrinking and

darkening from about 200° (Found : C, 76·2; H, 6·7; N, 8·6. $C_{21}H_{20}O_2N_2$ requires C, 75·9; H, 6·1; N, 8·4%). Light absorption : $\lambda_{max.}$ 2300, 3100, 3600 (log ε 4·06, 3·94, 4·07), $\lambda_{min.}$ 2800, 3300 Å (log ε 3·58, 3·86). After 4·5 hr. in solution : $\lambda_{max.}$ 2250, 2650, 3100, 3450, 3600, 4000 (log ε 4·16, 4·45, 4·45, 4·38, 4·38, 3·79), $\lambda_{min.}$ 2400, 2800, 3250, 3500, 3900 Å (log ε 3·95, 3·97, 4·31, 4·33, 3·75).

3 : 4 : 6 : 9-*Tetrahydro*-2″ : 3″-*dimethoxy*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (XI).—A mixture of the above, purified base (30 mg.), Adams catalyst (10 mg.), and acetic acid (10 c.c.) was shaken under hydrogen at room temperature and pressure. The theoretical volume of hydrogen was absorbed in about 10 min. and, after filtration, the solution was evaporated to dryness under reduced pressure. The residue was treated with water and sodium hydroxide solution. The precipitated base (m. p. 283—285°) crystallised from aqueous acetone as colourless needles, m. p. 294°, identical with the specimen prepared by the alternative method.

Action of Phosphoryl Chloride on 2-*Carboxy*-4 : 5-*dimethoxyphenyl*-N-(2′-3′-*indolylethyl*)*acetamide*.—A solution of the above homophthalamic acid (100 mg.) and phosphoryl chloride (2 c.c.) in toluene (5 c.c.) was refluxed for 40 min. A small amount of the product crystallised and, after evaporation to dryness (reduced pressure), the residue was dissolved in boiling methanol (charcoal). After concentration of the solution to a small volume, the product crystallised as orange needles, m. p. 262°. After several crystallisations from methanol the m. p. was raised to 273—274° alone or when mixed with 1-(2-chlorocarbonyl-4 : 5-dimethoxybenzylidene)-1 : 2 : 3 : 4-tetrahydro-β-carboline hydrochloride. The addition of sodium hydroxide solution to an aqueous solution of this product gave the corresponding lactam, lemon needles (from methanol), m. p. 290° (291—292° on admixture with an authentic specimen). Slightly impure lactam was isolated direct from the cyclisation by addition of alkali to the crude residue obtained on evaporation of the excess of phosphoryl chloride and solvent.

3-2′-(*Furfurylideneamino*)*ethylindole*.—Furfuraldehyde (6·0 g.) and tryptamine (10 g.) were mixed and stirred. With evolution of heat, the contents of the flask set solid within a minute. 3-2′-(*Furfurylideneamino*)*ethylindole* crystallised from aqueous alcohol (charcoal) as buff-coloured plates (13·5 g., 93%), m. p. 135° (Found : C, 76·0; H, 6·1; N, 11·7. $C_{15}H_{14}ON_2$ requires C, 75·6; H, 5·9; N, 11·8%). Absorption bands occur at 2·9 (NH) and 6·06 μ (C:N). When a solution of picric acid in ether was added to an ethereal solution of the base tryptamine picrate separated (Found : C, 49·7; H, 3·4. Calc. for $C_{16}H_{15}O_7N_5$: C, 49·4; H, 3·8%).

3-2′-(*Furfurylamino*)*ethylindole*.—3-2′-(Furfurylideneamino)ethylindole (5·0 g.), platinum dioxide (0·4 g., *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 463), and methanol (150 c.c.) were shaken together under hydrogen. The catalyst was reduced in 5 min. (80 c.c. of hydrogen) and hydrogen (520 c.c., 1 mol.) was absorbed in a further 50 min. The product was obtained as a nearly colourless, very viscous oil (4·3 g., 86%), b. p. 168°/0·06 mm. The *base* slowly crystallised and then separated from light petroleum as white needles, m. p. 56—57° (Found : C, 74·9; H, 7·2; N, 11·5. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7%). The *picrate*, prepared in alcohol, crystallised from benzene as irregular, orange prisms, m. p. 161° (Found : C, 54·0; H, 4·2; N, 15·0. $C_{21}H_{19}O_8N_5$ requires C, 53·7; H, 4·1; N, 14·9%). The *hydrochloride* crystallised from acetone–ether as irregular, cream prisms, m. p. 168° (Found : C, 65·0; H, 6·4; N, 10·0; Cl, 12·7. $C_{15}H_{17}ON_2Cl$ requires C, 65·2; H, 6·2; N, 10·1; Cl, 12·7%).

3-2′-(N-*Acetyl*-N-*furfurylamino*)*ethylindole*.—A mixture of 3-2′-(furfurylamino)ethylindole (5·0 g.) and acetic anhydride (6·4 g.) was refluxed for 15 min. and the solution poured on ice and neutralised with sodium carbonate. The *acetyl* derivative (5·8 g.) crystallised from aqueous acetone as irregular, white prisms, m. p. 102·5° (Found : C, 72·6; H, 6·6; N, 10·1. $C_{17}H_{18}O_2N_2$ requires C, 72·3; H, 6·4; N, 9·9%).

Attempted fission of the furan nucleus of this base by means of aqueous alcoholic hydrochloric acid and alcoholic hydrogen chloride was unsuccessful. Boiling glacial acetic acid brought about no change and boiling 50% hydrobromic acid in glacial acetic acid gave a tar.

N-*Furfurylidene*-2-*phenylethylamine*.—When furfuraldehyde (9·6 g.) was added to 2-phenylethylamine (12·1 g.) evolution of heat occurred and the mixture became red. After 15 minutes' heating on the steam-bath the *product* was isolated by means of ether and obtained (16·5 g., 83%) as a colourless oil, b. p. 94°/0·06 mm., n_D^{17} 1·6795, m. p. 33—34° (prisms from light petroleum) (Found : C, 78·5; H, 6·6; N, 7·4. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%).

N-*Furfuryl*-2-*phenylethylamine*.—*N*-Furfurylidene-2-phenylethylamine (2·0 g.) was hydrogenated in the presence of Adams catalyst (0·1 g.) in methanol (30 c.c.). Reduction of the catalyst occurred in 5 min. (20 c.c. absorbed) and the reduction stopped after 250 c.c. of hydrogen had been absorbed. N-*Furfuryl*-2-*phenylethylamine* (1·6 g., 80%) had b. p. 107°/0·06 mm., n_D^{17} 1·5500 (Found : C, 77·8; H, 7·6; N, 7·1. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%).

The *picrate*, prepared in alcohol, crystallised from water as irregular, yellow prisms, m. p. 133° (Found : C, 53·2; H, 3·9; N, 12·8. $C_{19}H_{18}O_9N_4$ requires C, 53·0; H, 4·2; N, 13·0%), and the 3 : 5-*dinitrobenzoate* from acetone as cream cubes, m. p. 165° (Found : C, 58·2; H, 4·8. $C_{20}H_{19}O_7N_3$ requires C, 58·1; H, 4·6%).

Furfurylideneacetophenone.—This was prepared by Drake and Gilbert's method (*J. Amer. Chem. Soc.*, 1930, **52**, 4966; cf. Semmler, *Ber.*, 1906, **39**, 729). The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as deep red rosettes, m. p. 161—162°, with previous shrinking (Found : C, 60·0, 60·2; H, 3·8, 4·0; N, 15·1. $C_{19}H_{14}O_5N_4$ requires C, 60·3; H, 3·7; N, 14·8%).

β-2′-*Furylpropiophenone.*—Furfurylideneacetophenone (5·0 g.) in methanol (50 c.c.) was hydrogenated in the presence of Raney nickel at atmospheric pressure and room temperature. Absorption of hydrogen (660 c.c., 10% excess) was complete in 15 min. β-2′-Furylpropiophenone (4·7 g., 94%) was obtained as a colourless oil, b. p. 92°/0·01 mm., n_D^{15} 1·5701, m. p. 36° (plates from light petroleum) (Found : C, 77·8; H, 6·2. Calc. for $C_{13}H_{12}O_2$: C, 78·0; H, 6·1%). Plattner *et al.* (*Helv. Chim. Acta*, 1935, **18**, 935) carried out the hydrogenation at 70° and found that 1·5 mols. of hydrogen were absorbed. They stated that their compound was impure but they obtained it crystalline (m. p. 37—37·5°). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as red needles, m. p. 144° (Found : C, 59·7; H, 4·2; N, 14·7. $C_{19}H_{16}O_5N_4$ requires C, 60·0; H, 4·2; N, 14·7%).

2-3′-*Phenylpropylfuran.*—β-2′-Furylpropiophenone (5·0 g.), diethylene glycol (30 c.c.), hydrazine hydrate (3 c.c. of 90%), and potassium hydroxide (3 g.) were refluxed together. After 90 min. the temperature was raised slowly to 200° and kept at 190—200° for 4 hr. 2-3′-Phenylpropylfuran was isolated by known methods as a mobile oil, b. p. 75—76°/0·01 mm., n_D^{17} 1·5318 (Plattner *et al.*, *loc. cit.*, give b. p. 134°/10 mm., n_D^{20} 1·5332; Semmler, *Ber.*, 1906, **39**, 729, reports b. p. 135°/10 mm., n_D 1·529) (Found : C, 83·6; H, 7·7. Calc. for $C_{13}H_{14}O$: C, 83·9; H, 7·6%). Light absorption : $\lambda_{max.}$ 2100, 2180 (log ε 4·01, 4·12), $\lambda_{min.}$ 2140 Å (log ε 3·98).

Oxidation of 2-3′-*Phenylpropylfuran by Means of Bromine in Methanol.*—A solution of bromine (0·5 c.c.) in methanol (10 c.c.) was added during 20 min. to a solution of the furan (1·8 g.) and fused potassium acetate (4·0 g.) in methanol (25 c.c.) with vigorous stirring at *ca.* 0°. The product was a pale yellow oil (1·2 g.), b. p. 96—100°/0·1 mm., n_D^{19} 1·5298 (Found : C, 77·5; H, 7·8. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%). Light absorption : $\lambda_{max.}$ 2140, 2550, 2650 (log ε 2·90, 2·76, 2·80), $\lambda_{min.}$ 2080, 2300, 2600 Å (log ε 2·75, 2·50, 2·70). This substance is possibly 2-*methoxy*-5-3′-*phenylpropylfuran.*

2-n-*Butylfuran.*—A mixture of 2-butyrylfuran (20·0 g.) (Gilman and Galloway, *J. Amer. Chem. Soc.*, 1933, **55**, 4197), diethylene glycol (240 c.c.), hydrazine hydrate (40 c.c. of 90%), and potassium hydroxide (43 g.) was refluxed for 2 hr. The temperature was raised slowly to 190—200°, the volatile fractions being collected. After 4 hr. at this temperature, the mixture was cooled, the distillate added to it, and the whole diluted with water. The 2-*n*-butylfuran was isolated by ether and obtained as a colourless, mobile oil with a pleasant odour (12 g., 67%), b. p. 140°, n_D^{25} 1·4460 (Gilman and Galloway, *loc. cit.*, give b. p. 137—138°, n_D^{25} 1·4460). Light absorption : $\lambda_{max.}$ 2120, 2250 (log ε 3·75, 3·88), $\lambda_{min.}$ 2160 Å (log ε 3·66).

2-*Butyl*-2 : 5-*dihydro*-2 : 5-*dimethoxyfuran.*—2-*n*-Butylfuran (1·2 g.) and fused potassium acetate (4·0 g.) in methanol (25 c.c.) were treated with bromine (0·5 c.c.) in methanol (10 c.c.) during 20 min. with stirring and cooling to about 0°. The *product* was a pale yellow, mobile oil with a pleasant, pear-like odour, b. p. 90—92°/14 mm., n_D^{20} 1·4510 (Found : C, 65·4; H, 9·3. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%). Light absorption : $\lambda_{max.}$ 2120, 2200, 2600 (log ε 3·41, 3·38, 3·41), $\lambda_{min.}$ 2100, 2160, 2400 Å (log ε 3·34, 3·31, 3·28). 2 : 5-Dihydro-2 : 5-dimethoxysylvan was prepared by bromine–methanol oxidation of sylvan (Clauson-Kaas and Limborg, *Acta Chem. Scand.*, 1947, **1**, 619), and had b. p. 79°/68 mm., n_D^{20} 1·4289 (Found : C, 58·2; H, 8·4. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·4%). Light absorption : $\lambda_{max.}$ 2080, 2140 (log ε 2·97, 2·96), $\lambda_{min.}$ 2100 Å (log ε 2·90).

2 : 5-*Dihydro*-2 : 5-*dimethoxyfurfuraldehyde Diacetate.*—Furfuraldehyde diacetate (39·8 g.) (Gilman and Wright, *Iowa State Coll. J. Sci.*, 1929, **4**, No. 1, 35) and fused potassium acetate (40·0 g.) were dissolved in methanol (300 c.c.) and a solution of bromine (10 c.c.) in methanol (200 c.c.) added during 40 min. at 19—20° with stirring. The greater part of the methanol was then removed under reduced pressure and a large volume of ether was added. The filtered solution was washed with a saturated solution of potassium hydrogen carbonate and with water and dried. The product distilled as a colourless, very viscous oil (20 g.), b. p. 122—130°/1·5 mm. (Clauson-Kaas and Fakstorp, *Acta Chem. Scand.*, 1947, **1**, 415, report b. p. 122—126°/1 mm.). On standing about 75% of the oil crystallised and the substance crystallised from methanol as prisms, m. p. 113° (Found : C, 51·2; H, 6·3. Calc. for $C_{11}H_{16}O_7$: C, 50·8; H, 6·2%). Light

absorption: $\lambda_{max.}$ 2060, 2180, 2500, 2550, 2950 (log ε 2·93, 2·87, 2·70, 2·70, 2·34), $\lambda_{min.}$ 2120, 2350, 2850 Å (log ε 3·61, 2·50, 2·26).

2 : 5-*Dihydro-5-methoxyfurfuraldehyde Diacetate*.—2 : 5-Dihydro-2 : 5-dimethoxyfurfuraldehyde diacetate (20·0 g.) in methanol (50 c.c.) was hydrogenated at room temperature and pressure in the presence of Raney nickel. The reduction stopped (*ca.* 6 hr.) after the theoretical volume of hydrogen (1870 c.c.) had been absorbed. 2 : 5-Dihydro-5-methoxyfurfuraldehyde diacetate was obtained as a colourless, mobile oil (14·0 g., 80%), b. p. 82—87°/0·06 mm., n_D^{23} 1·4508 (Found: C, 51·9, 51·8; H, 6·1, 6·2. $C_{10}H_{14}O_6$ requires C, 52·2; H, 6·1%). Light absorption: $\lambda_{max.}$ 2100, 2160, 2550, 2700 (log ε 3·54, 3·59, 2·89, 2·96), $\lambda_{min.}$ 2120, 2450, 2600 Å (log ε 3·48, 2·06, 2·80). On further catalytic reduction tetrahydrofurfuraldehyde diacetate was obtained as a mobile oil with a pleasant fruit-like odour, b. p. 124—126°/27 mm., n_D^{20} 1·4370 (Scheibler, Sotscheck, and Friese, *Ber.*, 1924, **57**, 1443, report b. p. 133°, $n_D^{20\cdot2}$ 1·4405) (Found: C, 53·1; H, 7·1. Calc. for $C_9H_{14}O_5$: C, 53·4; H, 7·0%); this showed no ultraviolet absorption.

Tetrahydrofurfuraldehyde, prepared from its acetate by hydrolysis with boiling dilute sulphuric acid, had b. p. 136—138°, n_D^{20} 1·4475 (Brenner, Coats, Robertson, and Allan, *J.*, 1949, S 25, give b. p. 145°/760 mm., n_D^{20} 1·4473). Its 2 : 4-dinitrophenylhydrazone separated from alcohol as orange needles, m. p. 133° (*idem*, *loc. cit.*, give m. p. 134°). The *dimedone derivative* was prepared in aqueous alcohol and crystallised from water as blades, m. p. 148°. For analysis it was sublimed at 117°/0·5 mm. (Found: C, 69·3; H, 8·8. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%).

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The Friedel–Crafts Reaction on 2-Methoxyfluorene and the Preparation of 7-Methoxyfluorenone-2-carboxylic Acid.

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In the Friedel–Crafts reaction with acetyl chloride in carbon disulphide solution 2-methoxyfluorene yields a mixture from which pure 2-acetyl-7-methoxyfluorene has been isolated. The orientation of the acetyl group has been confirmed by oxidation of the ketone to 7-methoxyfluorene- and thence to 7-methoxyfluorenone-2-carboxylic acid, which was synthesised from 2-amino-7-nitrofluorenone.

7-METHOXYFLUORENE-2-CARBOXYLIC ACID and 7-methoxyfluorenone-2-carboxylic acid were required for examination of their possible mesomorphic behaviour. Since the two-stage oxidation of 2-acetyl-7-methoxyfluorene should afford both acids, the Friedel–Crafts reaction on 2-methoxyfluorene was undertaken.

The preparation of 2-methoxyfluorene starts with nitration of technical fluorene (Kuhn, *Org. Synth.*, 1933, **13**, 74). The scale of the reduction to 2-aminofluorene (78—80%) by calcium chloride and zinc dust (Kuhn, *loc. cit.*) is limited by the large volume of the reactants. Much larger quantities of 2-nitrofluorene may be reduced in high yield by iron pin dust and hydrochloric acid, in alcohol. Ruiz (*Anal. Asoc. Quím. Argentina*, 1928, **16**, 225), Ray and Hull (*J. Org. Chem.*, 1949, **14**, 394), and Lothrop (*J. Amer. Chem. Soc.*, 1939, **61**, 2115) describe the preparation of 2-hydroxyfluorene in yields ranging from 20—90%, but in our hands the methods were not satisfactory.

When applied to 2-methoxyfluorene, the procedure adopted to prepare 4′-acetyl-4-methoxydiphenyl from 4-methoxydiphenyl (Gray, Hartley, and Brynmor Jones, *J.*, 1955, 1412) gave a mixture and isolation of 2-acetyl-7-methoxyfluorene was difficult: of thirty such reactions, twenty-five gave an average yield of 27% of the 7-acetyl derivative, but in five no pure product was isolatable. Attempts to obtain the other possible isomeric

ketones (1- and 3-acetyl-2-methoxyfluorene) from the mother-liquors gave impure fractions and yielded impure 2 : 4-dinitrophenylhydrazones. Fieser and Bradscher (*J. Amer. Chem. Soc.*, 1936, **58**, 1738), who first prepared 4-acetyl-4'-methoxydiphenyl from 4-methoxydiphenyl, isolated the isomeric 3-acetyl derivative, in unspecified yield, only after hydrolysis of its purified semicarbazone.

The constitution of 2-acetyl-7-methoxyfluorene was proved by oxidation to 7-methoxyfluorene-2-carboxylic acid which was then oxidised to 7-methoxyfluorenone-2-carboxylic acid. 2-Amino-7-methoxyfluorenone was then prepared, with some modification to the original methods (Gouldon and Kon, *J.*, 1945, 930; Eckert and Langecker, *J. prakt. Chem.*, 1928, **118**, 263). 2-Amino-7-methoxyfluorenone, whose constitution is established, was then converted into 2-cyano-7-methoxyfluorenone which on hydrolysis yielded the keto-acid and thence, by Wolff–Kishner reduction, the fluorenecarboxylic acid, both identical with the acids from the Friedel–Crafts product.

Experimental

M. p.s are corrected.

2-Nitrofluorene.—Technical fluorene (180 g.) was nitrated by Kuhn's method (*loc. cit.*), and the product crystallised from acetic acid, to give pale yellow needles, m. p. 158° (55—65%).

2-Aminofluorene.—To 2-nitrofluorene (62 g., 1 mol.), 90% ethanol (500 ml.), and concentrated hydrochloric acid (20 ml.), stirred on a boiling-water bath, iron pin dust (58 g., 3 atom-equiv.) was added gradually during 30 min. Heating was continued for at least 12 hr., then sodium carbonate (17 g.) was added, followed by a few drops of concentrated aqueous ammonia to alkalinity. Heating and stirring were continued for a further 45 min., the mixture was filtered hot (Whatman 541 paper), and the filtrate evaporated until crystallisation commenced. The light grey crystals of 2-aminofluorene, m. p. 127° (75%), were collected. This can be done on twice the above scale, but the yield is 67% owing to higher losses in the hot filtration. Kuhn (*loc. cit.*) records the m. p. 127·5°.

2-Hydroxyfluorene.—2-Aminofluorene (11 g., 1 mol.) was dissolved in boiling glacial acetic acid (240 ml.), the solution was allowed to cool to 80°, and boiling 40% w/w sulphuric acid (50 ml.) added quickly with stirring. Rapid cooling gave the very finely divided amine sulphate, which was diazotised in suspension by the dropwise addition of sodium nitrite (5 g., 1·2 mole) in water (50 ml.) during 20 min. Stirring was continued for a further 1·5 hr., at 0—5°. The excess of nitrite was destroyed by sulphamic acid. The suspension was diluted with water (70 ml.) and added in a thin stream to boiling 40% w/w sulphuric acid (250 ml.). Tar was produced, and, after 10 minutes' boiling, charcoal was added and the mixture filtered hot. 2-Hydroxyfluorene which crystallised from the filtrate was washed with dilute aqueous sodium hydrogen carbonate, dried, and crystallised from glacial acetic acid. The light brown crystals, m. p. 170·5°, were obtained in average yield of 45%. Ray and Hull (*loc. cit.*) give m. p. 169—171°.

2-Methoxyfluorene.—2-Hydroxyfluorene (30·2 g., 1 mol.) was stirred with a solution of sodium hydroxide (20·5 g., 3 mols.) in water (500 ml.), and heated to 70°. Methyl sulphate (42 g., 2 mols.) was added to the suspension of the sodium salt, and the temperature maintained at 70° for 30 min. The cooled alkaline suspension was filtered and the ether washed with water. Crystallisation from absolute ethyl alcohol gave nearly colourless plates of 2-methoxyfluorene, m. p. 109° (80%). Ruiz (*loc. cit.*) records the m. p. 108°.

2-Acetyl-7-methoxyfluorene.—To 2-methoxyfluorene (9·8 g., 1 mol.), dissolved in redistilled carbon disulphide (100 ml.), finely sieved, anhydrous aluminium chloride (8·1 g., 1·17 mol.) was added quickly. The mixture was stirred and the temperature kept at 3—4° during addition of redistilled acetyl chloride (4 ml., 1·1 mol.). The temperature was then raised to 45° for 45 min.; an orange-brown complex separated. The mixture was cooled and the complex decomposed by ice and concentrated hydrochloric acid (100 ml.). The solvent was removed by passing steam over the surface of the stirred mixture, whereafter the whole was cooled, and the grey solid mixture of ketones (11·3 g.; m. p. 64—110°) was collected. The solid was stirred twice for 10 min. with ether (40 ml.). After filtration and washing with ether (10 ml.), the solid crystallised from *iso*propyl alcohol (50 ml.), giving a pale yellow ketone, m. p. 98—114° (4·3 g.). The crystals passed in chloroform through activated alumina (10 × ¾"). Elution with chloroform gave a narrow band (dark) at the top of the column, followed by a broad yellow

band (green fluorescence), and a nearly colourless band (blue fluorescence). Elution was continued until the middle band reached the end of the column, the eluent was evaporated, and the colourless solid crystallised from *iso*propyl alcohol (then having m. p. 123—125°) and finally from methyl alcohol to give colourless plates (3·2 g.), m. p. 129·5—130·5° (27%). No other pure compound could be isolated from the column. Repeated crystallisation of the *2-acetyl-7-methoxyfluorene* from the above solvents gave a maximum m. p. of 134·5° (Found: C, 80·5; H, 5·6. $C_{16}H_{14}O_2$ requires C, 80·7; H, 5·9%). The deep red *2:4-dinitrophenylhydrazone* (Found: C, 63·0; H, 4·5; N, 13·4. $C_{22}H_{18}O_5N_4$ requires C, 63·15; H, 4·3; N, 13·4%) has m. p. 222°.

If the orange-brown complex is filtered directly from the cooled reaction mixture, sucked dry, and added with stirring to ice-cold concentrated hydrochloric acid, then triturated and crystallised from *iso*propyl alcohol as above, the 2-acetyl derivative (m. p. 123—125°) is obtained without chromatographic purification. The yield is however only 11%.

7-Methoxyfluorene-2-carboxylic Acid.—2-Acetyl-7-methoxyfluorene (8 g.) was dissolved in dioxan (200 ml.) at 45° and cooled quickly to 20° and treated during 10 min. with sodium hypobromite [from bromine (8 ml.), and sodium hydroxide (22·5 g.) in water (110 ml.)]. The temperature rose to about 30°, whereafter the mixture was warmed at 35—40° for 15 min. Sodium dithionite was added and the whole boiled 30 min. to steam-distil off most of the bromoform and dioxan. Sufficient water was added to dissolve the sodium salt at the b. p., and the solution was filtered hot, and acidified. The precipitate was collected, dried, sublimed at 170—180°/ <1 mm., and crystallised twice from xylene. *7-Methoxyfluorene-2-carboxylic acid* was obtained in 75% yield as slightly yellow needles, m. p. 267·5° (Found: C, 75·1; H, 4·9. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%). The acid is mesomorphic, exhibiting a nematic phase which becomes isotropic at 294° with slight decomposition.

7-Methoxyfluorenone-2-carboxylic Acid.—7-Methoxyfluorene-2-carboxylic acid (0·4 g.), sodium dichromate (5 g.), and acetic acid (100 ml.) were refluxed for 4 hr. The solution was cooled and diluted with an equal volume of water, and the orange precipitate collected. The *7-methoxyfluorenone-2-carboxylic acid* was dissolved in warm, dilute sodium hydroxide and the solution filtered hot. The filtrate was acidified and the orange gelatinous precipitate filtered off and dried. Two crystallisations from nitrobenzene gave orange prisms (0·35 g., 83%), m. p. 344° (decomp.) (Found: C, 71·0; H, 4·0. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%). The *amide* crystallised from nitrobenzene as orange needles, m. p. 291—292° (Found: C, 71·0; H, 4·5; N, 5·5. $C_{15}H_{11}O_3N$ requires C, 71·1; H, 4·3; N, 5·5%).

2-Nitrofluorenone.—Oxidation of 2-nitrofluorene by Diels's method (*Ber.*, **1901**, **34**, 1760) gave 2-nitrofluorenone, m. p. 225° (72%), after crystallisation from nitrobenzene.

2-Aminofluorenone.—2-Nitrofluorenone (60 g.), hydrated stannous chloride (240 g.), concentrated hydrochloric acid (300 ml.), and acetic acid (600 ml.) were stirred for 30 min. on a boiling-water bath. The reaction is exothermic. The mixture was cooled, and the hydrochloride collected, washed with water, and stirred with 2N-sodium hydroxide (600 ml.) for 10 min. The solid was filtered off when cold, and crystallised from ethanol, giving deep red prisms of 2-aminofluorenone, m. p. 160·5° (41 g., 78%). Diels (*loc. cit.*), who used ammonium polysulphide, records m. p. 160°.

2-Amino-7-nitrofluorenone.—2-Aminofluorenone was nitrated on a 30-g. scale by Gouldon and Kon's method (*loc. cit.*), but it was beneficial to the yield to keep the reaction mixture at room temperature for at least 24 hr. Highly efficient cooling is necessary when the nitration mixture is poured on ice. Crystallisation from nitrobenzene gave blue-black needles, m. p. 287—288° (80—85%). Eckert and Langecker (*loc. cit.*) record m. p. 279°.

2-Hydroxy-7-nitrofluorenone.—2-Amino-7-nitrofluorenone (30 g.) was readily diazotised and hydrolysed by Gouldon and Kon's method (*loc. cit.*). The product crystallised from nitrobenzene in 68—74% yield as red plates, m. p. 305—306°.

2-Methoxy-7-nitrofluorenone.—Methylation must be effected in weak alkali. 2-Hydroxy-7-nitrofluorenone (38·5 g., 1 mol.), sodium hydroxide (8 g., 1 mol.), and water (770 ml.) were heated to 70—80°, and methyl sulphate (20 g., 1 mol.) was added with stirring. After 30 min. at 80°, more methyl sulphate (1 mol.) and aqueous sodium hydroxide were added alternately in small portions, the mixture being kept just alkaline. When cold, the brown solid was separated, dried, and crystallised from nitrobenzene–chlorobenzene (250 : 50 ml.). The brown crystals, m. p. 247·5—249·5°, were obtained in 70% yield. Eckert and Langecker (*loc. cit.*) record m. p. 248·5—249·5°.

2-Amino-7-methoxyfluorenone.—2-Methoxy-7-nitrofluorenone (33 g.), acetic acid (330 ml.), concentrated hydrochloric acid (165 ml.), and hydrated stannous chloride (132 g.) were stirred

on a boiling-water bath for 1 hr. When cold, the red solid was collected, washed with concentrated hydrochloric acid, boiled for 10 min. with 2N-potassium hydroxide (330 ml.), and cooled. The product, m. p. 193—195° (92%), crystallised from chlorobenzene as permanganate-coloured needles, m. p. 194·5° (21·5 g., 71%). Eckert and Langecker (*loc. cit.*), who used sodium polysulphide, record m. p. 195—196°.

2-Cyano-7-methoxyfluorenone.—2-Amino-7-methoxyfluorenone (2·25 g., 1 mol.) was dissolved in boiling glacial acetic acid (25 ml.), and hot 2N-sulphuric acid (30 ml.) added, and the whole rapidly cooled to 0°. Sodium nitrite (0·8 g., 1·15 mol.) in water (5 ml.) was added at 0—5°, and the mixture stirred for 30 min. After the first 10 min., a dark red solution was obtained, and then the crystalline, purple-red diazo-sulphate separated. This was collected and added in small portions to a solution of potassium nickelocyanide [potassium cyanide (3·6 g.) in water (40 ml.) was added to a solution of nickel sulphate (3 g.) in water (40 ml.)] at 90°. A light brown solid separated, and the suspension was boiled until nitrogen evolution was complete. The crude *2-cyano-7-methoxyfluorenone* was collected, dried, and sublimed at 170—180°/1 mm. Crystallisation from chlorobenzene yielded orange, felt-like needles, m. p. 205° (1·2 g., 50%) (Found: C, 76·5; H, 4·0; N, 5·8. $C_{15}H_9O_2N$ requires C, 76·6; H, 3·8; N, 5·95%).

Initially the more soluble amine hydrochloride was diazotised and treated as above. Crystallisation of the sublimate from glacial acetic acid gave orange needles, m. p. 156° (50%). Analysis showed this material to be 2-chloro-7-methoxyfluorenone (Found: 68·7; H, 3·4; Cl, 13·8. Calc. for $C_{14}H_9O_2Cl$: C, 68·7; H, 3·7; Cl, 14·5%), containing 3—4% of the nitrile, from which it could not be completely separated.

7-Methoxyfluorenone-2-carboxylic Acid.—The nitrile (1 g.), in a hot mixture of acetic acid (40 ml.), concentrated sulphuric acid (40 ml.), and water (30 ml.), was refluxed for 3 hr. The acid which separated was washed with water and crystallised from nitrobenzene in orange prisms, m. p. 344° (decomp.) (0·95 g., 86%) (Found: C, 71·0; H, 4·0%).

7-Methoxyfluorene-2-carboxylic Acid.—7-Methoxyfluorenone-2-carboxylic acid (1 g.), 5% sodium ethoxide in absolute ethyl alcohol (16 ml.), and 100% hydrazine (2 ml.) were heated at 170° for 8 hr. Care must be taken not to allow the reactants to splash on to the walls while filling the tube, as this causes evaporation and formation of an orange solid which is not reduced out of contact with the reaction mixture. When cold, the colourless solid was filtered off and washed with a little warm water. The sodium salt was dissolved in boiling water (200 ml.) and filtered hot, and the filtrate acidified. The colourless precipitate was collected, dried, sublimed at 170—180° at <1 mm., and crystallised twice from xylene. Pale straw needles of 7-methoxyfluorene-2-carboxylic acid, m. p. 167·5° (80%), were obtained (Found: C, 75·1; H, 5·1%). The upper transition point of the nematic phase was again 294°, with slight decomposition.

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Pteridine Studies. Part VII. The Degradation of 4-, 6-, and 7-Hydroxypteridine by Acid and Alkali.*

By Adrien Albert.

[Reprint Order No. 6156.]

Hot dilute acid and alkali readily degraded 4-hydroxypteridine (I) to 2-aminopyrazine-3-carboxylic acid (II) and its amide; acid also gave rise to 2-aminopyrazine. 7-Hydroxypteridine gave 4 : 5-diaminopyrimidine with alkali, but dilute acid unexpectedly isomerized it to 6-hydroxypteridine.

6-Hydroxypteridine was degraded to 4 : 5-diaminopyrimidine by boiling solutions buffered between pH 6 and 10. There was no action below this range, but above it an extraordinary disproportionation occurred, giving 6 : 7-dihydroxypteridine and 7 : 8-dihydro-6-hydroxypteridine. Under defined conditions the last-named combined with unchanged 6-hydroxypteridine to give two dipteridyls. Ammonia gave a dipteridylamine. Hydroxylamine added across the 7 : 8-double bond of 6-hydroxypteridine to give (finally) 7-amino-6-hydroxypteridine, and it is suggested that this reaction provides a clue to the mechanism of the disproportionation and dimerizations.

It has been shown that the monohydroxypteridines are, as a class, much more labile than their polyhydroxy-analogues (Albert, Brown, and Cheeseman, *J.*, 1952, 4219), the criteria being the percentages remaining after an hour's refluxing with N-sulphuric acid and N-sodium hydroxide. The nature and quantity of the principal decomposition products have now been determined.

(I) (II)

4-Hydroxypteridine (I).—Acid decomposition produced 2-aminopyrazine-3-carboxylic acid (II), its amide, and 2-aminopyrazine, in the amounts given in Table 1. Identification was made by mixed melting points and comparison of ultraviolet spectra. The amide was determined by quantitative paper chromatography, developed in water. The amide had the lowest R_F of the four spots; the remaining three spots (the other two pyrazines and

Table 1. *Hydrolysis of* 4-*hydroxypteridine* (2 *hours at* 100°) *with* N-H_2SO_4 (3 *equiv.*) *or* N-NaOH (2 *equiv.*)

			Acid hydrolysis (details)				Alkaline hydrolysis (summary)
			$d_{1\,cm.}$				
2-Aminopyrazine	$\gamma_{max.}$ (mμ)	log ε	Unknown (4×10^{-5}M)	Standard (2×10^{-5}M)	Recovery (%) of standard	Yield (%) of product	Yield (%) of product
(Unsubstituted) as cation	325	3·77	0·113	0·105	90 *	53·8	0
-3-carboxylic acid	340	3·76	0·082	0·118	103	34·8	61
-3-amide	350	3·80	0·011	0·126	100	4·4	6
	246	4·06	0·020	0·227	98	4·4	—

* Complete recovery could be obtained at pH 1 (instead of 2), but the higher acidity interfered with the electrophoresis.

uncharged starting material) were too close to one another, in this and all other solvents tried, for this technique to be used. However, the other pyrazines were conveniently determined by quantitative paper electrophoresis. From the pK values, it was concluded that pH 5·8 would be suitable for uniquely moving 2-aminopyrazine-3-carboxylic acid to the anode [pK_a = 3·70 (basic); < 1 (acidic)]. This was confirmed by a trial run on a mixture of the four substances concerned. The process was then applied to the hydrolysis

* Part VI, S. F. Mason, *J.*, 1955, 2336.

mixture, and the relevant spot was eluted, and analysed as in quantitative paper chromatography (for details of both processes see Experimental section). Similarly, at pH 2·0, 2-aminopyrazine ($pK_a = 3·14$) was uniquely moved to the cathode and analysed.

Alkaline decomposition of 4-hydroxypteridine produced the same acid and amide, but no 2-aminopyrazine (see Table 1). Much 4-hydroxypteridine remained but this could not be determined directly, because it was invisible under the 365-mμ lamp and, although visible, was rapidly photo-decomposed under the 254-mμ lamp. No other spots were found.

7-Hydroxypteridine.—Here again, the oxygen-bearing ring was readily opened by acid and alkali. After 4 hours in N-potassium hydroxide at 100°, 42% of 4 : 5-diaminopyrimidine was found by quantitative paper chromatography. This substance was isolated (35%) from the reaction mixture, together with unchanged 7-hydroxypteridine (40%). The latter could not be determined chromatographically, because of its photosensitivity at 254 mμ.

In dilute mineral acids at 37° 7-hydroxypteridine was converted in 5 days into 6-hydroxypteridine in 85% yield. The course of this reaction is apparently: hydrolysis to glyoxylic acid and 4 : 5-diaminopyrimidine (which was detected in the mother-liquor) and re-combination to 6-hydroxypteridine. The latter reaction is known to be favoured by low pH values (Albert, Brown, and Cheeseman, *J.*, 1952, 1620). The identity of the product was confirmed by comparison of all the following properties with material prepared from 2-chloro-4-glycinyl-5-nitropyrimidine, an unambiguous synthesis (Albert *et al.*, *J.*, 1952, 1620): elementary analysis, basic pK_a and hysteresis loop on titration, ultraviolet spectra of cation and of neutral molecule, also the infrared spectrum. The most convenient synthesis of 6-hydroxypteridine has been the condensation of 4 : 5-diaminopyrimidine with ethyl glyoxylate in 2N-sulphuric acid at 20° for 18 hours (Albert *et al.*, *J.*, 1952, 1620), giving 65% of the 6-isomer mixed with 20% of the 7-isomer. The above isomerization indicated that it would be better to conduct the condensation at 37° for 5 days, and an 85% yield of pure 6-hydroxypteridine was obtained in this way.

6-Hydroxypteridine.—The reactions of the substance commonly known as 6-hydroxypteridine become clearer if it is borne in mind that it is a pseudo-acid (cf. Albert, Ciba Symposium on the Chemistry and Biology of Pteridines, Churchill, London, 1954, p. 210), and can be converted into the sodium salt of the true acid only after a slow chemical change. This is evident from the hysteresis loop traced out in titration, the addition of alkali giving pH values much higher than those found on back-titration (Albert *et al.*, *J.*, 1952, 1620). No other monoydroxypteridine behaves thus. The anhydrous sodium salt (described below) is normal, but the pseudo-acid, which retains one molecule of water in excess of $C_6H_4ON_4$ up to 180° (where it begins to darken), has a spectrum indicating less conjugation than the other monohydroxylated dihydropteridine. It may well be a dihydroxylated dihydropteridine.

The ionic state of 6-hydroxypteridine in the experiments now to be described has been calculated from the pK_a values for this substance (Albert, Brown, and Cheeseman, *J.*, 1952, 1620) by the equation: Percent ionized $= 100/[1 + \text{antilog}\ (pH - pK_a)]$. Below pH 2, the "pseudo-acid" is the cation ($pK_a = 3·7$) and at pH 5, the neutral molecule of a weak acid ($pK_a = \sim 9·7$). Above pH 5 it enters into slow equilibrium with the anion of the true acid ($pK_a = 6·7$) which can be isolated only as a salt. At pH 7·2 this stronger acid is 75% ionized, but much of the pseudo-acid is also present (non-ionized). At pH 9·2, the ionization of the stronger acid is 99% complete, but only at pH 11 is the pseudo-acid completely converted into the stronger one.

Recognition and separation of the products of decomposition of 6-hydroxypteridine were facilitated by the R_F values and ionization constants assembled in Table 2, and infrared spectra helped to establish identity and purity.

6-Hydroxypteridine was unchanged when refluxed with N-sulphuric acid (1 hour), or with buffer at pH 5 (7 hours). Thus, the cation and the neutral molecule of the pseudo-acid are stable to hydrolysis by H^+. However, refluxing (7 hours) with buffers at pH 7·2 and 9·2 produces, respectively, 34 and 11% of 4 : 5-diaminopyrimidine, with about 1% of 7-hydroxypteridine. No other products were detected, and the unchanged 6-hydroxypteridine was easily recovered at pH 5·5 where it is sparingly soluble. These figures

suggest that the neutral molecule of one of the acids is susceptible to hydrolysis by OH^-.

At pH 10·5, no 4 : 5-diaminopyrimidine was formed. Instead, a new reaction occurred, one not involving degradation of the pteridine skeleton. This reaction was more conveniently studied at higher pH's, and hence discussion of this experiment is deferred to p. 2693.

TABLE 2. *Ionization and chromatographic data used in recognizing and separating products related to 6-hydroxypteridine.*

			Paper chromatography [a] R_F and colour of spot under u.v. lamps					
			Developed in butanol–acetic acid (7 : 3) [f]			Developed in 3% ammonium chloride [p]		
No.	Substance [a]	pK_a	R_F	254 mμ	365 mμ	R_F	254 mμ	365 mμ
	Pyrimidine							
1	4 : 5-Diamino-	6·0 [b]; <0	0·30	D	X	0·65	D	X
2	4-Amino-5-hydroxyacetamido-	(*ca.* 6)	0·20	D	X	0·75	D	X
3	5-Amino-4-carboxymethylamino-	3 [c]; 6·5 [b]	0·15—0·20 [e]	D	X	0·80	D	X
	Pteridine							
4	6-Hydroxy-	3·7 [b]; 6·7 [c,d]	0·25 [h]	B	X	0·45 [m]	B	X
			0·35—0·80	D	X	0·05	D	X
5	7-Hydroxy-	1·2 [b]; 6·4 [c]	0·50	D	X	0·65 [j]	D	X
				B [n]	B		B [n]	B
6	6 : 7-Dihydroxy-	<2 [b]; 6·9 [c]; 10 [c]	0·25 [i]	B	V	0·45 [i]	B	V
7	7 : 8-Dihydro-6-hydroxy-	4·8 [b]; 10·5 [c]	0·30 [j]	D	X	0·45 [i]	D	X
8	7-Amino-6-hydroxy-	See Table 3	0·20 [k]	DV	V	0·30 [k]	DV	V
	Various							
9	8-Hydroxymethylpurine	Table 3	0·45	D	X	0·65 [j]	D	X
10	Substance O	0 [b]; >9 [c]	0·05	Y	Y	O	Y	Y
11	Substance P	<3 [b]; >7 [c]	0·15 [l]	D	X	O	D	X

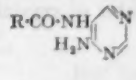
B = Blue fluorescence. D = Dark, against fluorescent background of paper (*i.e.*, absorption without fluorescence). DV = Intermediate between D and V. V = Violet fluorescence. X = Invisible. Y = Yellow fluorescence.

[a] Dissolved in cold 0·1N-sodium hydroxide except No. 2 (water) and 10 (KOH; solution must be used within 5 min. of preparation). [b] Basic. [c] Acidic. [d] See text. [e] Ascending method. R_F's differ from those obtained by the descending method (Albert *et al.*, *J.*, 1952, 1620). [f] pH = 2·7. [g] Streak caused by slow ring-closure in acidic solvent. [h] This spot arises from incipient disproportionation, and is seen only if the compound is kept alkaline. [i] Coincides with No. 4. [j] Coincides with No. 1. [k] Streaks back to origin. [l] Spot is crescent-shaped with the horns pointing downwards. [m] The 0·45 spot may arise from incipient disproportionation and is not seen when working below 20°. When eluted and reapplied, each spot generates the two spots. [n] Change due to photodecomposition after exposure (254 mμ) for a few seconds. [p] pH = 5·5.

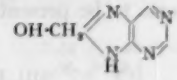
When dissolved in N-sodium hydroxide 6-hydroxypteridine quickly deposited the normal sodium salt which in the solid state was stable at 110° and kept for 6 months at room temperature also in 0·01M-aqueous solution (pH 9) for three days at 20°. When a suspension of the salt in N-sodium hydroxide was left at 20°, the 6-hydroxypteridine all disappeared by the fifth day, its place being taken by 7 : 8-dihydro-6-hydroxy- and 6 : 7-dihydroxypteridine, isolated in 40% and 45% yields respectively (the only other substance present was apparently a dipteridyl, provisionally called substance P, in 8% yield). This reaction is a disproportionation of 6-hydroxypteridine into a product with one more oxygen atom and another with two more hydrogen atoms, and differs from previous disproportionations of hydroxy-heterocyclic compounds where one product loses one oxygen atom and the other loses two hydrogen atoms (*e.g.*, *N*-methyl-5-hydroxyacridan, Albert, "The Acridines," Edward Arnold and Co., London, 1951, p. 187; hydrastinine, McGeogh and Stevens, *J.*, 1934, 1465; cotarnine, Ingold, "Structure and Mechanism in Organic Chemis'try," Bell, London, 1953, p. 580).

It was at first thought that this disproportionation may proceed by ring-opening to the pyridine aldehyde (III*a*) followed by a Cannizzaro reaction. If this were so, 4-amino-5-hydroxyacetamidopyrimidine (III*b*) should cyclize in cold N-sodium hydroxide to

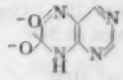
7 : 8-dihydro-6-hydroxypteridine. However, it was found that this pyrimidine, prepared from glycollic acid and 4 : 5-diaminopyrimidine, gave only 8-hydroxymethylpurine (IV) and 4 : 5-diaminopyrimidine, when thus treated. Hence the disproportionation proceeds without ring-opening by attack of a hydroxyl ion on the anion of 6-hydroxypteridine (no neutral molecules are present at this high pH). It is unlikely to be a nucleophilic attack, because that would be expected to occur at position 4 (electron-density diagrams of pteridine show the 4-position to be much poorer than the 7-position in electrons, and the presence of the 6-hydroxy-anion should increase this difference; cf. Albert, *Quart. Rev.*, 1952, **6**, 213). It is more likely that a hydroxyl ion adds across the double bond, to give



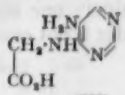
(III) (*a*) R = CHO
(*b*) R = CH_2·OH



(IV)



(V)



(VI)

the ion (V) [the 7 : 8-bond has the highest degree of double-bond character in the pteridine nucleus, according to recent calculations by C. A. Coulson and T. H. Goodwin (personal communication)]. It is then supposed that the ion (V) transfers a hydride ion from the 7-position to a molecule of starting material which becomes (a dianion of) 7 : 8-dihydro-6-hydroxypteridine, a process which necessarily converts (V) into (an anion of) 6 : 7-dihydroxypteridine.

Another reaction was found which presumably involves an addition across the 7 : 8-double bond : the formation of 7-amino-6-hydroxypteridine from 6-hydroxypteridine and hydroxylamine. The new substance was readily hydrolysed to 6 : 7-dihydroxypteridine by acid or alkali.

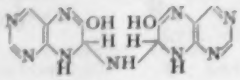
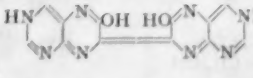
Disproportionation of 6-hydroxypteridine in boiling N-sodium hydroxide was complete in 15 minutes, but gave only 6 : 7-dihydroxypteridine (35% isolated) and substance P (52% isolated). The latter is evidently formed by combination between the 7 : 8-dihydro-6-hydroxypteridine (which in the 20° experiment is largely protected by the poor solubility of its sodium salt at that temperature) and unchanged 6-hydroxypteridine. This is readily shown by the formation of substance P (25%) from these two substances in 0·1N-sodium hydroxide at 20° in 2 days (at this dilution of alkali, the products of disproportionation are barely detectable before 3 days). Substance P is not formed from either 6-hydroxypteridine or the 7 : 8-dihydro-derivative under these mild conditions: both must be present. Likewise it is not formed from the pyrimidine (VI) (see below) and 6-hydroxypteridine under these conditions.

When 7 : 8-dihydro-6-hydroxypteridine was boiled with N-sodium hydroxide for 1½ hours, the ring opened to give 5-amino-4-carboxymethylaminopyrimidine (VI), which rapidly recyclizes in cold 0·1N-hydrochloric acid. These reactions are similar to those given by 5 : 6-dihydro-7-hydroxypteridine (Albert *et al.*, *J.*, 1952, 1620). None of this pyrimidine (VI) was present after the hot disproportionation of 6-hydroxypteridine, 7 : 8-dihydro-6-hydroxypteridine being removed, as substance P, faster than it can be hydrolysed.

The action of boiling 2N-sodium carbonate on 6-hydroxypteridine is similar to that of sodium hydroxide, but much slower. After 4 hours the products were 6 : 7-dihydroxypteridine (15%), substance P (25%), unchanged starting material (32%), and a new reddish-orange dipteridyl, provisionally called substance O (12%). No 4 : 5-diaminopyrimidine or 7 : 8-dihydro-6-hydroxypteridine could be detected.

Ammonia behaved differently: a solution of 6-hydroxypteridine in 2N-ammonia rapidly deposited large yellow crystals of the ammonium salt, but within 5 minutes these began to change into a white, amorphous precipitate (substance N). Analyses indicated a formula $(C_6H_4ON_4)_2NH_3$, and when gently warmed with N-hydrochloric acid or 0·1N-sodium hydroxide the substance gave 6-hydroxypteridine (90% yield) and ammonia. However, substance N is not a salt or loosely bound adduct of ammonia and 6-hydroxypteridine, because none of the latter could be detected by paper chromatography. Also, substance N did not dissolve in boiling acetic acid, in which 6-hydroxypteridine is very soluble.

Dr. S. F. Mason reports that substance N shows 8 bands (in the "fingerprint region" of the infrared) that are present in neither 6-hydroxypteridine nor its sodium salt; also there is a strong carbonyl band near 1600 cm.$^{-1}$. The most likely constitution seems to be that of the dipteridylamine (VII), formed by the addition of one molecule of ammonia across the 7 : 8-double bond of 6-hydroxypteridine to give 7-amino-7 : 8-dihydro-6-hydroxypteridine and further reaction of this with another molecule of 6-hydroxypteridine. This mechanism receives support from the formation of 7-amino-6-hydroxypteridine instead of substance N when an oxidizing agent is present. Less attractive would be the formulation of substance N as an analogue of (*a*) diacetonamine or (*b*) dibarbiturylmethylamine (Möhlau and Lither, *J. prakt. Chem.*, 1906, **73**, 475); these would require respectively one and two of the oxygen atoms to be present as water of crystallisation, but water is not evolved even at 240°.

(VII)   (VIII)

The orange substance, $C_{12}H_8O_2N_8$ (substance O), is formed when 6-hydroxypteridine is refluxed with (*a*) 2N-sodium carbonate (0% in 30 minutes, 5% in one hour, 12% in 4 hours), (*b*) aqueous hydroxylamine (5% in 30 minutes), or (*c*) M-ammonium hydrogen sulphide (50% in 10 minutes). The helpful role of reducing conditions is explained by the increased yield obtained when 6-hydroxypteridine and 7 : 8-dihydro-6-hydroxypteridine were refluxed together in 2N-sodium carbonate (18% in 30 minutes); the dihydro-compound alone was ineffective. It may be supposed that the 7-methylene group in the dihydropteridine adds across the 7 : 8-double bond of 6-hydroxypteridine to give 7 : 8 : 7′ : 8′-tetrahydro-6 : 6′-dihydroxy-7 : 7′-dipteridyl, which loses two hydrogen atoms to give substance O (VIII).* This 7-methylene group proved active enough to couple with diazotized sulphanilic acid.

Substance O could not be reduced by hydrogen over platinum at 20°, sodium amalgam, sodium borohydride, sodium dithionite, or tin and acid. In cold 0·1N-potassium hydroxide it rapidly absorbed oxygen from the air, giving two equivalents of 6 : 7-dihydroxypteridine. When air was excluded, a ruby-red dipotassium salt was formed. Substance O is unaffected by boiling N-hydrochloric acid. No water was lost at 250°. Formula (VIII) with its long conjugated pathway, two acidic groups, and lack of benzenoid character (regained on oxidation) fits these facts well. Unfortunately, as with substances N and P, the poor solubility prevented determination of molecular weight.

Substance P ($C_{12}H_{10}O_2N_8$) also is formed by the union of 6-hydroxy- and 7 : 8-dihydro-6-hydroxy-pteridine (see above). This reaction is reversible, for when the substance is boiled with 0·1N-sodium hydroxide, traces of 6-hydroxy- and 7 : 8-dihydro-6-hydroxypteridine were obtained (boiling with water or N-hydrochloric acid was ineffective). It is a diacidic base, and the fact that it is a stronger acid than substance O was used in their separation. Substance P does not auto-oxidize in alkaline solution. Chemical oxidation did not produce substance O, but gave two equivalents of 6-hydroxypteridine. It is suggested, in analogy with the action of hydroxylamine (see p. 2697), that the NH-group of 7 : 8-dihydro-6-hydroxypteridine has added across the 7 : 8-double bond of 6-hydroxypteridine to give 7 : 8 : 7′ : 8′-tetrahydro-6 : 6′-dihydroxy-7 : 8′-dipteridyl (IX). The corresponding 8 : 8′-dipteridyl which is a symmetrical hydrazine is less likely in view of low $\lambda_{max.}$ (Table 3). An analogy exists between the formation of substance P and alloxantin, but the latter is a glycol (Beilstein's Handbuch, 4th Ed., 2nd. Supp. *XXVI*, 335) whereas P is an acid. Nor is P likely to be formed by an aldol-like condensation, because neither 6-hydroxypteridine nor the 7 : 8-dihydro-derivative condenses with benzaldehyde in 0·1N-sodium hydroxide (2 days at 20°).

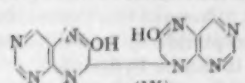

(IX)

Table 3 lists some physical constants of substances described in this paper. The similarity of the spectra of 8-hydroxymethylpurine to those of 8-methylpurine (Mason,

* The hydrogen atoms have been placed at positions 3 : 3′ to give the longest conjugated pathway, but could conceivably be 1 : 1′ or 8 : 8′.

J., 1954, 2072) assisted identification and sharply differentiated this substance from the isomers, 5 : 6-dihydro-7- and 7 : 8-dihydro-6-hydroxypteridine (Albert *et al.*, *J.*, 1952, 1620).

TABLE 3.

Substance	Solubility in H_2O (100°), 1 in	pK_a (in H_2O), spread, and concn. (20°)	Spectrophotometry in H_2O: $\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$ (mol.)	pH
7-Amino-6-hydroxypteridine	5000	—	233; 310; 323; 339	4·01; 4·24; 4·35; 4·16	4·8; 6·0
anion	—	(about 8)	241; 329; 343	4·20; 4·29; 4·20	10; 13
5-Amino-4-carboxymethylaminopyrimidine	30	—	290	4·05	4·74 [d]
cation	—	6·54 ± 0·07 (0·03M)	—	—	1 [e]
anion	—	2·9 [a]	253; 289	3·88; 3·85	8·8
8-Hydroxymethylpurine	14	—	266	4·01	6·1
cation	—	2·62 ± 0·02 (0·02M)	265	3·94	0
anion	—	8·79 ± 0·01 (0·02M)	275	4·01	11·4
Substance N	20,000	—	—	—	—
Substance O	>100,000	—	—	—	—
cation	—	(about 1) [b]	297; 419; 445	3·81; 4·63; 4·63	0
anion	—	—	460; 490 [c]	—	13
Substance P	>100,000	—	—	—	—
cation	—	—	292	4·33	1
anion	—	—	299	4·30	13

[a] Approximate, because of tendency for ring to close in acid. [b] Determined spectrometrically. [c] Only approximate because of rapid oxidation, even in de-aerated solvent and covered cells. [d] At this pH, 97% is zwitterionic. [e] Ring-closure to 7 : 8-dihydro-6-hydroxypteridine is rapid at this pH.

EXPERIMENTAL

Microanalyses were by Mr. P. R. W. Baker, Beckenham. The yields of substances that lack a m. p. refer to the stage at which they became chromatographically homogeneous (on paper). All substances were dried at 120°, unless otherwise specified.

Hydrolysis of 4-Hydroxypteridine.—4-Hydroxypteridine (0·1482 g.; Albert, Brown, and Cheeseman, *J.*, 1951, 474) was refluxed with N-sulphuric acid (3 ml., 3 equiv.) or N-sodium hydroxide (2 ml.) for 2 hr., then diluted to 60 ml., and added to 0·01M-phosphate buffer (10 ml.; pH 6). This solution was adjusted to pH 6, and then diluted to 100 ml. (thus it became 0·01M with reference to 4-hydroxypteridine). 0·005M-Solutions were prepared from 2-aminopyrazine, its 3-carboxylic acid, and the corresponding amide, adjusted to the same pH and same content of phosphate and sulphate. Care was taken to choose a pH where only one ionic species could be present. For determination of the amide (by paper chromatography), the digest and the standard (0·02 ml. of each) were applied separately with an " Agla " micrometer syringe to a 24" sheet of Whatman No. 1 filter paper, 1" above the lower edge. This was developed with water (ascending method). The dried chromatograms were examined in light of λ 254 mμ (Thermal Syndicate's lamp T/M5/369E, with Chance Brothers' filter OX7/19874). The standard and the unknown spots were marked in pencil and cut out as strips 1" × 4½", with the spot near to one end which tapered to a point. A blank strip in the same R_F area was also cut out. These three strips were separately eluted with 0·1N-hydrochloric acid as described by Brimley and Barrett (" Practical Chromatography," London, Chapman and Hall, 1953). The eluates (2—3 ml.) were diluted to 5 ml. and examined in a Hilger " Uvispek " photoelectric spectrophotometer at $\lambda_{max.}$ (the eluate from the blank strip was used in the reference cell). The results are given in Table 4. The experiment was run (in duplicate) in the dark to avoid contamination with the photolytic products of 4-hydroxypteridine.

For the determination of 2-aminopyrazine and its 3-carboxylic acid (by paper electrophoresis), the digest and a 0·005M-standard (0·02 ml. of each) were similarly applied (1" apart) to the central line of a No. 1 Whatman paper. Buffer solution (phosphate pH 2·00 and 5·80 respectively) was allowed to rise by capillarity from both ends of the paper. When the two fronts had met, the current (2·6 mA, 220 v, direct) was passed for 3½ hr. The paper was dried at 110° for 5 min. and the spots were outlined in pencil under 365-mμ light (an ordinary Woods lamp). The standard, blank, and unknown strips were cut out as above, eluted overnight

with 0·1N-hydrochloric acid (for 2-aminopyrazine) or with 0·01M-phosphate buffer of pH 6·0 (for the carboxylic acid), and examined as above. The results are given in Table 1.

Alkaline Hydrolysis of 7-Hydroxypteridine.—7-Hydroxypteridine (Albert *et al.*, *J.*, 1952, 1620) was refluxed with N-potassium hydroxide, under the conditions used for the 4-isomer. The resulting solution was adjusted to pH 3·0 with N-sulphuric acid and diluted to 100 ml. A 0·005M-solution of 4 : 5-diaminopyrimidine was prepared with the same pH and concentration of potassium sulphate. These were applied to papers (as above), two of which were developed by chromatography in 3% aqueous ammonium chloride, and two in *n*-butanol (2 vols.)–5N-acetic acid (1 vol.). Brief examination under the 254-mμ lamp, which is somewhat destructive for 4 : 5-diaminopyrimidine, enabled the spots to be marked, and they were eluted and submitted to spectrophotometry as above. The results are given in Table 4.

TABLE 4. *Alkaline hydrolysis of 7-hydroxypteridine to 4 : 5-diaminopyrimidine.*

Developer	$\lambda_{max.}$ (mμ)	log ε	$d_{1\ cm.}$ Unknown (4×10^{-5}M)	$d_{1\ cm.}$ Standard (2×10^{-5}M)	Recovery (%) of standard	Yield (%) of product
Ammonium chloride (3% aq.) ...	284	3·937	0·120	0·138	80 *	44
Butanol–5N-AcOH (2 : 1)	,,	,,	0·110	0·142	82	39

* 4 : 5-Diaminopyrimidine is sensitive to the wavelength (254 mμ) used to render the spot visible.

Recovery of 7-Hydroxypteridine and 4 : 5-Diaminopyrimidine.—After a similar alkaline hydrolysis, but with N-sodium hydroxide, the solution was cooled to 20° and the pure sodium salt of 7-hydroxypteridine filtered off after 10 min. The filtrate was adjusted to pH 10 with sodium hydrogen carbonate and evaporated to dryness. The residue was exhaustively extracted with alcohol, and the extract decolorized (carbon) and concentrated, giving pale 4 : 5-diaminopyrimidine, m. p. and mixed m. p. 200—201°.

Action of Acid on 7-Hydroxypteridine.—7-Hydroxypteridine (1 g.; fine powder) and 2N-sulphuric acid (15 ml., 4·5 equiv.) were set aside at 37° for 5 days. The solution was decolorized with acid-extracted charcoal. Sodium citrate (2 g.) was added and enough 6N-sodium hydroxide to give pH 5·5. The deposit of 6-hydroxypteridine (0·93 g.) was chromatographically homogeneous (on paper). It was recrystallized from 230 parts of water (Found: for material dried at 120°/0·1 mm.: C, 43·2; H, 3·5; N, 33·7. Calc. for $C_6H_4ON_4,H_2O$: C, 43·4; H, 3·6; N, 33·7%).

6-*Hydroxypteridine* (*Recommended Synthesis*).—4 : 5-Diaminopyrimidine (11 g.), ethyl glyoxylate hemiacetal (20 g., 1·3 equiv.; Rigby, *J.*, 1950, 1912) and 2N-sulphuric acid (180 ml.) were kept at 37° for 5 days. The dark solution was shaken with acid-washed carbon (1 g.). The filtrate was taken to pH 5·5 with sodium citrate (10 g.) and 10N-sodium hydroxide (about 11 ml.). The precipitate was refluxed with water (100 ml.) and filtered at the b. p., then recrystallized from 240 parts of boiling water (yield 85% of monohydrate). [6-Hydroxypteridine monohydrate (dried at 110°) is to be understood in all the following preparations where "6-hydroxypteridine" is mentioned.]

Action of Buffer Solutions on 6-Hydroxypteridine.—6-Hydroxypteridine (0·083 g., 0·0005 mole) was refluxed with 0·05M-buffers (20 ml.; acetate pH 5·00, phosphate pH 7·20, borate pH 9·18) for 7 hr. All solutions remained clear. They were adjusted to pH 2·0 with N-hydrochloric acid (because precipitates were formed at intermediate values) and diluted to 50 ml. with 0·01N-hydrochloric acid. They were submitted to paper-electrophoresis (see under 4-hydroxypteridine, above) in pH 4·00 acetate buffer (0·1M), with 4 : 5-diaminopyrimidine (0·005M) as standard. Brief examination under the 254-mμ lamp showed that the 4 : 5-diaminopyrimidine cation (pK_a 6·0) had run much further than the 6-hydroxypteridine. Strips of paper were cut, as before, and eluted, and the eluate measured spectrometrically. The recovery of the standard was 80—84% from these papers, and the calculations were based on this.

Sodium Salt of 6-Hydroxypteridine.—N-Sodium hydroxide (10 ml., 2 equiv.) was added to 6-hydroxypteridine (0·83 g.), suspended in water (5 ml.). The solution deposited yellow crystals of the *sodium salt* which were filtered off after an hour at 0°, washed with alcohol, and dried at 110° (0·8 g.) (Found, for material dried at 110° and 0·01 mm. and burnt over V_2O_5: C, 42·3; H, 2·5; N, 33·25. $C_6H_3ON_4Na$ requires C, 42·4; H, 1·8; N, 33·0. Gain, on exposure, to const. wt.: 17·8%. $C_6H_3ON_4Na,2H_2O$ requires 17·5%).

Action of Cold Sodium Hydroxide Solution.—6-Hydroxypteridine (2·5 g., 0·015 mole), dissolved in cold N-sodium hydroxide (30 ml., 2 equiv.), was stored at 20° for 5 days. The suspension was clarified by warming to 50°. The solution was taken to pH 2 (metanil-yellow) with

5N-sulphuric acid (8 ml.), and filtered after an hour at 20°. The precipitate of **6** : 7-dihydroxypteridine (1·1 g.) recrystallized from 300 parts of water (Found: C, 43·6; H, 2·2; N, 34·7. Calc. for $C_6H_4O_2N_4$: C, 43·9; H, 2·45; N, 34·2%). The filtrate was adjusted to pH 8·5 [$(HO{\cdot}CH_2)_3C{\cdot}NH_2$; 0·5 g.]* and N-sodium hydroxide (12 ml.), and filtered. The precipitate was rapidly recrystallized (as the sodium salt) from boiling N-sodium hydroxide (15 ml.), dissolved in hot water (12 ml.), and adjusted to pH 8·5, giving **7** : 8-dihydro-6-hydroxypteridine (0·88 g.), which recrystallized from 400 parts of water (Found: C, 48·2; H, 4·4; N, 36·6. Calc. for $C_6H_6ON_4$: C, 48·0; H, 4·0; N, 37·3%). The identity of these two substances with unambiguously synthesized material (Albert *et al.*, *J.*, 1952, 1620) was further confirmed by comparison of ionization constants and ultraviolet and infrared spectra. The filtrate from the sodium salt was adjusted to pH 5 with acetic acid and filtered at 100°. The precipitate was recrystallized (as *substance P dihydrochloride*) from N-hydrochloric acid (9 parts) giving large prisms (0·27 g.) (Found, for material dried at 20°/0·1 mm.: C, 35·7; H, 4·0; O, 15·8; N, 27·6; Cl, 17·4. $C_{12}H_{10}O_2N_8,2HCl,2H_2O$ requires C, 35·4; H, 4·0; O, 15·7; N, 27·5; Cl, 17·4%). The crystals were dissolved in 12 parts of boiling 0·1N-hydrochloric acid and adjusted to pH 5 with sodium citrate and hydroxide. The free *base* was filtered off at the b. p. It was insoluble in all solvents tried, and remained unchanged at 350° (Found, for material dried at 120°: C, 48·3; H, 3·4; N, 37·3. $C_{12}H_{10}O_2N_8$ requires C, 48·3; H, 3·4; N, 37·6%). There was no loss on drying further at 150°. More data on substance P are on p. 2698.

4-*Amino*-5-*hydroxyacetamidopyrimidine* (III*b*).—**4** : 5-Diaminopyrimidine (0·90 g.; Brown, *J. Appl. Chem.*, 1952, **2**, 239), glycollic acid (cryst.; 1·9 g., 3 equiv.), and water (3 ml.) were heated in an open vessel at 100° for 6 hr. Phosphate buffer (2 ml.; 0·1M; pH 7) was added, then 2N-sodium carbonate until the pH at 100° was 7·5. The product was evaporated and extracted with boiling alcohol (30 ml.). The extract deposited **4** : 5-diaminopyrimidine (0·5 g.) on refrigeration, and the filtrate from this, concentrated *in vacuo* to 3 ml., deposited **4**-*amino*-5-*hydroxyacetamidopyrimidine* (0·1 g.), decomp. ~150° to 8-hydroxymethylpurine (Found: C, 42·2; H, 4·7; N, 33·7. $C_6H_8O_2N_4$ requires C, 42·8; H, 4·8; N, 33·3%). It was not quite homogeneous chromatographically, but on attempted recrystallization it partly cyclized to 8-hydroxymethylpurine.

8-*Hydroxymethylpurine* (IV).—Higher yields of this substance were obtained as follows. Ethyl glycollate (13 g., 4 equiv.) and **4** : 5-diaminopyrimidine (3·3 g.) were heated in an open flask at 140° for 2 hr. The excess of ester was recovered *in vacuo*, and the residue recrystallized from water (25 ml.; carbon). The filtrate (pH 3) was adjusted to pH 5·5 before cooling, and yielded 8-*hydroxymethylpurine* (60%), m. p. 262° (effervescence), soluble in 220 parts of cold water. It recrystallized from 200 parts of alcohol (Found: C, 48·2; H, 3·7; N, 37·5. $C_6H_6ON_4$ requires C, 48·0; H, 4·0; N, 37·3%).

7-*Amino*-6-*hydroxypteridine*.—Hydroxylamine hydrochloride (0·84 g., 2 equiv.) was added to a solution of 6-hydroxypteridine (1 g.) and sodium carbonate (1·3 g.) in water (50 ml.). The mixture was refluxed for 30 min. and filtered at 100° from substance O (0·05 g., see below). The filtrate was adjusted to pH 5·5 with sodium citrate and 5N-sulphuric acid, warmed to 100°, and filtered. The colourless precipitate of 7-amino-6-hydroxypteridine (65%) was dissolved in N-sodium hydroxide (2 equiv.) and refrigerated. The *sodium salt* was washed with alcohol and air-dried at 20° (Found: C, 32·5; H, 3·7; N, 31·7. $C_6H_4ON_5Na,2H_2O$ requires C, 32·6; H, 3·6; N, 31·7%). This was dissolved in 100 parts of boiling water and acidified to pH 5·5, and the almost colloidal *base* was collected. It becomes brown about 315° without melting, and is poorly soluble in organic solvents (Found: C, 44·4; H, 3·0; N, 42·3. $C_6H_5ON_5$ requires C, 44·2; H, 3·1; N, 42·9%). It was completely hydrolysed to **6** : 7-dihydroxypteridine when refluxed with 2 equivalents of N-sodium carbonate (1 hr.), N-sodium hydroxide (10 min.), or N-hydrochloric acid (5 min.).

Action of Sodium Hydroxide at 100°.—6-Hydroxypteridine (1·66 g., 0·01 mole) and N-sodium hydroxide (20 ml., 2 equiv.) were gently refluxed for 15 min., adjusted to pH 9·0 with glycine (0·3 g.) and 5N-sulphuric acid, and filtered at 100°. The residue (crude substance P) was purified through the hydrochloride as above (0·86 g.). The filtrate was taken to pH 4 with sodium citrate (0·3 g.) and 5N-sulphuric acid, and filtered after chilling, giving pure **6** : 7-dihydroxypteridine (0·5 g.)

5-*Amino*-4-*carboxymethylaminopyrimidine* (VI).—**7** : 8-Dihydro-6-hydroxypteridine (0·9 g.) and N-sodium hydroxide (12 ml., 2 equiv.) were refluxed for 90 min., cooled, and seeded with

* Buffers of suitable p*K* were used here and elsewhere to sharpen the separations and increase the yields. Trial experiments were conducted which established that they did not initiate chemical change.

the sodium salt of the starting material (0·15 g. recovered by filtration). The filtrate was placed in an ice-bath and carefully brought to pH 5 with acetic acid, and the precipitated *5-amino-4-carboxymethylaminopyrimidine* (75%) recrystallized from 30 parts of water (Found: C, 43·0; H, 4·8; N, 33·6. $C_6H_8O_2N_4$ requires C, 42·9; H, 4·8; N, 33·3%). There was no apparent change at 300°, but chromatography showed that the substance had completely cyclized (no decarboxylation). In 0·1N-hydrochloric acid (2 equiv.) at 20°, ring closure was half-complete in about 1 hr., and complete in 6 hr. (determined by neutralizing and chromatographing samples in ammonium chloride solution); the 7 : 8-dihydro-6-hydroxypteridine was isolated at pH 8·5 (95%).

Synthesis of Substance P from Components.—6-Hydroxypteridine (0·34 g.) and 7 : 8-dihydro-6-hydroxypteridine (0·30 g.) in 0·1N-sodium hydroxide (80 ml.) were left at 20° for 2 days. The clear solution was boiled, adjusted to pH 5, and filtered at 100°. The precipitate was purified through the hydrochloride as above (yield, 0·15 g.).

Action of Sodium Carbonate.—6-Hydroxypteridine (0·5 g., 0·003 mole) and 2N-sodium carbonate (15 ml., 10 equiv.) were refluxed for 4 hr. (pH was 10·5 at start and finish), filtered from substance O (0·06 g., see below) and cooled, then substance P (0·11 g.) was filtered off. The filtrate was adjusted to pH 2·0 (metanil-yellow) with sulphuric acid and filtered at once from 6 : 7-dihydroxypteridine (0·08 g.). The filtrate was adjusted to pH 5·5 (sodium citrate and hydroxide) and chilled and the 6-hydroxypteridine (0·16 g.) filtered off.

Reaction with Ammonia.—6-Hydroxypteridine (0·82 g.) was dissolved in 2N-ammonia (40 ml., 30 equiv.) at 35°, and set aside at 20°. Next day, the suspension was gently refluxed for 5 min. and filtered at the b. p., giving *substance N* (0·3 g.) as a white powder. The filtrate was refluxed again next day and deposited 0·1 g. more. The filtrate from this, brought to pH 5·5, gave 6-hydroxypteridine (0·4 g.). None of the usual products of alkaline decomposition was formed. Substance N is insoluble in all solvents, and in cold 0·1N-sodium hydroxide or hydrochloric acid. It becomes brown at 270° without melting [Found: C, 46·0; H, 3·4; N, 39·5. $(C_6H_4ON_4)_2,NH_3$ requires C, 46·0; H, 3·5; N, 40·3%].

When substance N (0·25 g.) was refluxed with N-hydrochloric acid (5 ml., 3 equiv.) for 5 min., and the solution adjusted to pH 5·5, 6-hydroxypteridine (0·24 g.) was obtained. Similar treatment with 0·1N-sodium hydroxide, but for 30 sec. only, gave 6-hydroxypteridine (0·23 g.).

Potassium ferricyanide (0·33 g., 1 equiv.) and 6-hydroxypteridine (0·08 g.) were dissolved, in that order, in 2N-ammonia (4 ml.) and set aside at 20° for 2 days. The solution was adjusted to pH 5·5. The precipitate, dissolved in N-sodium hydroxide, gave the sodium salt of 7-amino-6-hydroxypteridine (0·06 g., 55%; dried at 20°; dihydrate).

Substance O.—6-Hydroxypteridine (1 g.) and M-ammonium hydrogen sulphide (60 ml., 10 equiv.) were refluxed for 10 min. and filtered at the b. p. giving substance O (0·5 g.). The filtrate contained 7-amino-6-hydroxypteridine (0·2 g.) and a precursor of substance O, which produces it (0·2 g.) when acidified to pH 5 and exposed to air. It was shown by infrared spectra to be identical with the two specimens prepared by other methods (see above). This substance, recrystallized from cold N-potassium hydroxide (2 equiv.) as the *dipotassium salt* (long ruby needles), which was washed with alcohol, and dried at 20°/0·01 mm. (Found: C, 35·1; H, 2·7; N, 27·5; loss at 120°, 9·4. $C_{12}H_6O_2N_8K_2,2H_2O$ requires C, 35·3; H, 2·5; N, 27·45; loss, 8·8. Found, for material dried at 120°: C, 38·6; H, 2·2. $C_{12}H_6O_2N_8K_2$ requires C, 38·7; H, 1·6%). It was suspended in water, adjusted to pH 7 with phosphoric acid, boiled for 5 min., and filtered at 100°, giving *substance O* as reddish-orange crystals (Found: C, 48·3; H, 2·8; N, 37·5. $C_{12}H_8O_2N_8$ requires C, 48·6; H, 2·7; 37·8%). It is unchanged at 350°. It is insoluble in 2N-ammonia, or organic solvents. The solution in 0·1N-sodium hydroxide is glutinous. The salts with mineral acids are lemon-yellow and highly insoluble (the hydrochloride requires 7000 parts of boiling N-hydrochloric acid to dissolve it: ten-fold dilution with water partly liberates the neutral molecule).

Substance P.—Two syntheses of this substance have already been given. It was not formed when 6-hydroxypteridine and 5-amino-4-carboxymethylaminopyrimidine (0·08 g. of each) were set aside at 20° in 0·1N-sodium hydroxide (20 ml.) for 2 days.

0·1M-Potassium permanganate (4·4 ml., equiv. to 2H) was added dropwise, at 20°, to substance P (0·2 g.), and kieselguhr (0·05 g.) in 0·1N-sodium hydroxide (28 ml.). The insoluble material was extracted with boiling water (3 ml.), and the combined filtrates were adjusted at once to pH 5·5; pure 6-hydroxypteridine (0·2 g.) was precipitated.

Substance P (0·08 g.) in 0·1N-sodium hydroxide (10 ml.) was unchanged at 20° for 27 hr., but when it was refluxed therein for an hour, paper chromatography clearly revealed spots characteristic of 6-hydroxypteridine and 7 : 8-dihydro-6-hydroxypteridine. After 2 hours'

refluxing with N-sodium hydroxide (4 equiv.), a spot characteristic of 6 : 7-dihydroxypteridine (arising from disproportionation of 6-hydroxypteridine) also appeared.

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The Synthesis of L-glycero*Tetrulose and Related Compounds.**

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L-*glycero*Tetrulose (L-erythrulose) has been prepared from D-fructose by two different routes. Syntheses of 5-deoxy-D-*threo*pentulose and 5 : 6-dideoxy-D-*threo*hexulose are also described. An attempted synthesis of L-*glycero*tetrulose 4-phosphate proved of little value as a preparative method.

RECENT investigations have indicated the importance of tetroses in photosynthesis (Bassham, Benson, Kay, Harris, Wilson, and Calvin, *J. Amer. Chem. Soc.*, 1954, **76**, 1760) and in pentose phosphate metabolism (Horecker, Gibbs, Klenow, and Smyrniotis, *J. Biol. Chem.*, 1954, **207**, 393). The enzyme transketolase involved in these processes acts on various ketose substrates, including L-*glycero*tetrulose, to give rise to "active glycollaldehyde." This term is used to describe the two-carbon moiety that is transferred from hydroxypyruvate or from $C_{(1)}$ and $C_{(2)}$ of L-*glycero*tetrulose, D-fructose 6-phosphate, D-*altro*heptulose 7-phosphate, and D-*erythro*pentulose 5-phosphate, respectively, to aldoses by transketolase with thiamine pyrophosphate as coenzyme. Thus, from D-ribose 5-phosphate, the product is D-*altro*heptulose 7-phosphate, which contains two more carbon atoms than its aldose precursor. Methods for preparing tetruloses, and in particular their phosphate derivatives, have thus attracted our attention.

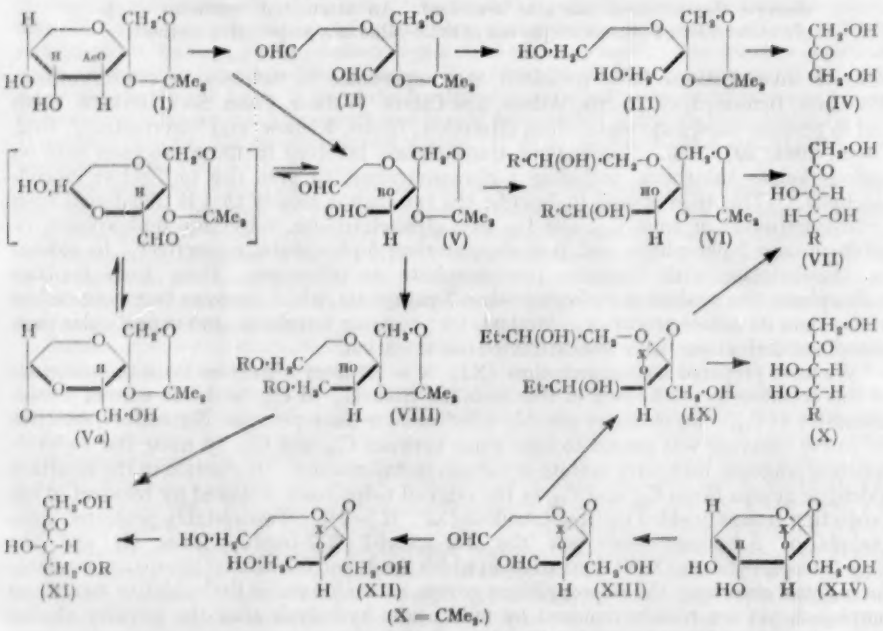
We have prepared L-*glycero*tetrulose (XI; R = H) from D-fructose since the structure of this tetrulose is pre-formed in this hexulose from $C_{(1)}$ to $C_{(4)}$, with the correct stereochemistry at $C_{(3)}$. By choice of suitably substituted D-fructopyranose derivatives, selective oxidative cleavage was caused to take place between $C_{(4)}$ and $C_{(5)}$ by using the α-glycol-splitting reagents, lead tetra-acetate or sodium metaperiodate. Reduction of the resultant aldehyde groups (from $C_{(4)}$ and $C_{(5)}$ of the original D-fructose), followed by removal of the protecting groups, yielded L-*glycero*tetrulose (XI; R = H). Two suitably protected compounds of D-fructopyranose are the 3-*O*-acetyl-1 : 2-*O*-*iso*propylidene (I) and the 2 : 3-*O*-*iso*propylidene (XIV) derivative, in which the 4- and 5-hydroxyl groups are available for α-glycol cleavage; the *iso*propylidene groups are stable under the oxidative conditions employed, yet are readily removed by mild acidic hydrolysis after the primary alcohol groups have been formed by reduction of the dialdehyde.

L-*glycero*Tetrulose (XI; R = H) has been prepared by bacterial oxidation of *meso*-erythritol (Bertrand, *Ann. Chim. Phys.*, 1904, **3**, 206, 259; Müller, Montigel, and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 1468; Whistler and Underköfler, *J. Amer. Chem. Soc.*, 1938, **60**, 2507) whereas oxidation with chemical reagents gives DL-*glycero*tetrulose (Fenton and Jackson, *J.*, 1899, **7**; Neuberg, *Ber.*, 1902, **35**, 2627; Deniges, *Annalen*, 1909, **18**, 149, 168; Fischer and Tafel, *Ber.*, 1887, **20**, 1090). The latter was synthesised by Raphael (*J.*, 1952, 401) from but-2-ene-1 : 4-diol, and Iwadare (*Bull. Chem. Soc. Japan*, 1939, **14**, 131) synthesised the D-isomer *via iso*propylidene-D-glyceroyl chloride and the corresponding diazo-ketone. No wholly chemical synthesis of the L-isomer has been recorded.

* A summary of this paper was submitted at the 126th meeting of the American Chemical Society, New York, September 1954.

3-*O*-Acetyl-1 : 2-*O*-*iso*propylidene-β-D-fructopyranose (I) was prepared from 1 : 2-4 : 5-di-*O*-*iso*propylidene-β-D-fructose in improved yield (cf. Ohle and Schultz, *Ber.*, 1938, **71**, 2302) by acetylation with acetic anhydride in pyridine followed by selective hydrolysis of the product with 80% aqueous acetic acid at 37°. In an attempt to prepare the mono-*O*-acetyl dialdehyde (V; R = Ac), this derivative was oxidised with an excess of aqueous sodium metaperiodate, but further oxidation occurred with loss of the acetyl group to give the dialdehyde (II) (but see below). Reduction of this with ethereal lithium aluminium hydride gave the diol (III) which on acidic hydrolysis yielded dihydroxyacetone (IV) instead of the required L-*glycero*tetrulose (XI; R = H). Oxidation of 3-*O*-acetyl-1 : 2-*O*-*iso*propylidene-β-D-fructopyranose (I) with 1 mol. of metaperiodate gave a mixed product since on reduction and acidic hydrolysis a mixture of dihydroxyacetone (IV) and L-*glycero*tetrulose (XI; R = H) was obtained.

Oxidation of 3-*O*-acetyl-1 : 2-*O*-*iso*propylidene-β-D-fructopyranose (I) with lead tetra-acetate in glacial acetic acid produced, in poor yield, a crystalline hydroxy-dialdehyde (V; R = H) (from which a bis-2 : 4-dinitrophenylhydrazone was prepared), rather than the expected mono-*O*-acetyldialdehyde (V; R = Ac), owing to deacetylation during isolation. This " dialdehyde " (V; R = H) existed in a modified form, however, since it was almost



unoxidised by aqueous sodium metaperiodate, reacted with only slightly over 1 mol. of sodium hypoiodite, and gave an infrared absorption (in Nujol mull) devoid of carbonyl characteristics, thus suggesting that it exists mainly as the bicyclic hemiacetal (V*a*) (cf. Hurd, Baker, Holysz, and Saunders, *J. Org. Chem.*, 1953, **18**, 186). Reduction of this compound with an excess of ethereal lithium aluminium hydride gave the triol (VIII; R = H) which consumed 1 mol. of sodium metaperiodate with formation of 0·88 mol. of formaldehyde. Acidic hydrolysis of the triol (VIII; R = H) gave a mixture of L-*glycero*-tetrulose (XI; R = H) and ethylene glycol, from which the latter was removed by continuous chloroform-extraction.

It was of interest to attempt the preparations of 5-deoxypentuloses and 5 : 6-dideoxyhexuloses as reference compounds in enzymic syntheses. Thus, the " dialdehyde "

(V; R = H) when treated with ethereal methylmagnesium iodide and with ethereal ethylmagnesium bromide, gave, after acid hydrolysis, products containing mainly syrupy 5-deoxy-D-*threo*pentulose (VII; R = Me) and syrupy 5 : 6-dideoxy-D-*threo*hexulose (VII; R = Et) respectively. On paper chromatograms they gave single spots with R_F values and colour reactions indistinguishable from those of authentic specimens. Derived phenylosazones were indistinguishable from those prepared from 5-deoxy-D-xylose and 5 : 6-dideoxy-D-*xylo*hexose respectively. Authentic 5 : 6-dideoxy-D-*threo*hexose phenylosazone was prepared from 5 : 6-dideoxy-D-*xylo*hexose obtained by the acid hydrolysis of 5 : 6-dideoxy-1 : 2-*O*-*iso*propylidene-D-*xylo*hexose (McSweeney and Wiggins, *Nature*, 1951, **168**, 874). Clearly, in the Grignard reactions, asymmetric syntheses occurred which favoured the formation of the D-*threo*- (VII) rather than the L-*erythro*-configurations (X).

As an additional route for the preparation of L-*glycero*tetrulose (XI; R = H), 2 : 3-*O*-*iso*propylidene-β-D-fructopyranose (XIV), obtained by selective acid hydrolysis of 2 : 3-4 : 5-di-*O*-*iso*propylidene-β-D-fructose (Ohle and Koller, *Ber.*, 1924, **57**, 1566; Wolfrom, Shilling, and Binkley, *J. Amer. Chem. Soc.*, 1950, **72**, 4544) was oxidised with excess of sodium metaperiodate in aqueous solution. Continuous extraction with chloroform gave the syrupy dialdehyde (XIII) which gave a crystalline bis-2 : 4-dinitrophenylhydrazone and was reduced by ethereal lithium aluminium hydride to the triol (XII). Acidic hydrolysis of this triol gave syrupy L-*glycero*tetrulose (XI; R = H), characterised as its phenylosazone. This method of preparation gave a higher yield of L-*glycero*tetrulose than the foregoing preparation, and is more convenient.

These preparations provide methods for the synthesis of the sugar labelled with ^{14}C; thus [1-^{14}C]D-fructose would give [1-^{14}C]L-*glycero*tetrulose, and [3 : 4-$^{14}C_2$]D-fructose would give [3 : 4-$^{14}C_2$]L-*glycero*tetrulose.

Reaction of the dialdehyde (XIII) with ethylmagnesium bromide did not appear to be as stereospecific as the similar reaction with the hydroxy-dialdehyde (V; R = H). Treatment of the dialdehyde (XIII) (obtained by oxidation of 2 : 3-*O*-*iso*propylidene-β-D-fructopyranose) with ethereal ethylmagnesium bromide, followed by acid hydrolysis of the product (IX), gave a material which behaved like a 5 : 6-dideoxyhexulose on paper chromatograms. Since the optical rotation of this material differed from that of 5 : 6-dideoxy-D-*threo*hexulose and the derived 5 : 6-dideoxyhexose phenylosazone had a low indefinite m. p., it was probably a mixture of 5 : 6-dideoxy-L-*erythro*- (X; R = Et) and 5 : 6-dideoxy-D-*threo*-hexulose (VII; R = Et).

A preparation of L-*glycero*tetrulose 4-phosphate was attempted. L-*glycero*Tetrulose 1-phosphate has been produced from formaldehyde and hexose diphosphate by a rat-liver preparation (Charalampous and Mueller, *J. Biol. Chem.*, 1953, **201**, 161) and may act as a source of active glycolaldehyde. The triol (VIII; R = H) was treated in pyridine with 2 molar equivalents of diphenyl phosphorochloridate (Foster, Overend, and Stacey, *J.*, 1951, 980), which reacts preferentially with primary alcohol groups, giving the di(diphenyl phosphate) [VIII; R = $PO(OPh)_2$]. Catalytic hydrogenation in the presence of barium carbonate gave the barium diphosphate (VIII; R = PO_3Ba), which was hydrolysed in acid to a mixture, very probably of L-*glycero*tetrulose 4-phosphate (XI; R = PO_3Ba) and 2-hydroxyethyl dihydrogen phosphate, as indicated by their rates of movement and colour reactions on paper chromatograms. The yield of tetrulose phosphate was so poor that separation was not attempted. Alternative routes are being explored.

Experimental

Unless otherwise stated, optical rotations were measured at 20° in H_2O, evaporations were carried out under reduced pressure, and the solvent and spray reagents used for paper chromatography were butan-1-ol–ethanol–water (40 : 11 : 19 v/v) and a *ca.* 4% solution of *p*-anisidine hydrochloride in butan-1-ol–water. Rates of movement of spots on paper chromatograms were related to those of rhamnose, galactose, or the solvent front, and are denoted by R_{Rh}, R_{Gal}, and R_F respectively.

3-O-*Acetyl*-1 : 2-O-iso*propylidene*-β-D-*fructopyranose* (I).—1 : 2-4 : 5-Di-*O*-*iso*propylidene-α-D-fructose (112 g.) in pyridine (600 c.c.) containing acetic anhydride (150 c.c.) was kept at 37° for 16 hr., then poured into water (1 l.). The precipitated syrup was taken up in chloroform and

washed with successive portions of aqueous sodium hydrogen carbonate, N-sulphuric acid, and water, dried ($MgSO_4$), filtered, and evaporated. The syrupy 3-*O*-acetyl-1 : 2-4 : 5-di-*O*-*iso*propylidene-β-D-fructose was selectively hydrolysed at 37° for 20 hr. in 80% aqueous acetic acid (720 c.c.). The solution was evaporated until a white solid separated. Light petroleum (b. p. 60—80°; 500 c.c.) was added and the resulting precipitate filtered off (49 g.). The filtrate was evaporated to a syrup and hydrolysed with 80% aqueous acetic acid (500 c.c.) as described above (yield 29 g.). A third hydrolysis yielded a further 13 g. Recrystallisation of the combined material from benzene–light petroleum (b. p. 60—80°) gave the desired product (I) (85 g.), m. p. 149°, $[\alpha]_D$ −153° (*c*, 1·35) (Found: C, 50·4; H, 6·9. Calc. for $C_{11}H_{18}O_7$: C, 50·4; H, 6·9%).

Oxidation of 3-O-*Acetyl*-1 : 2-O-*isopropylidene*-β-D-*fructopyranose* (I).—(a) *With sodium metaperiodate.* The acetate (I) (0·5 g.) in phosphate buffer (pH 6) containing 0·15M-sodium metaperiodate (35 c.c.) was set aside for 48 hr. and then the solution was extracted thrice with ether. The combined extract was dried ($MgSO_4$) and filtered. The oxidation product was reduced in dry ethereal solution by an excess of lithium aluminium hydride (Lythgoe and Trippett, *J.*, 1950, 1983), and the product hydrolysed with 0·2N-sulphuric acid at 100° for 1 hr. After neutralisation ($BaCO_3$), filtration, and evaporation, the optically inactive product gave on paper chromatograms one discrete spot corresponding to dihydroxyacetone.

In a similar experiment, using 1 molar equivalent of sodium metaperiodate, the final product on examination on paper chromatograms showed the presence of dihydroxyacetone (IV) and *glycero*tetrulose (XI; R = H).

(b) *With lead tetra-acetate.* The acetate (I) (20 g.) in acetic acid (200 c.c.) was shaken with lead tetra-acetate (44 g., 1·3 mol.) for 24 hr. After treatment with ethylene glycol (0·82 c.c.), the solution was evaporated at 25° to *ca.* 100 c.c. It was added to water (500 c.c.), neutralised ($BaCO_3$), and filtered, and the filtrate extracted thrice with equal volumes of chloroform. The chloroform extract was dried ($MgSO_4$), filtered, and evaporated to a syrup which crystallised. Recrystallisation twice from ether gave the "*dialdehyde*" (V; R = H) (6·7 g.) as long prisms, m. p. 140—141°, $[\alpha]_D$ −37° (*c*, 0·94 in $CHCl_3$), −28° (*c*, 1·12) (Found: C, 49·7; H, 6·4%; *M*, 227, 226, as determined by the Menzies–Wright ebullition method, in chloroform and benzene respectively. $C_9H_{14}O_6$ requires C, 49·5; H, 6·4%; *M*, 218). The aldehyde (50 mg.) in ethanol (5 c.c.) containing 2 : 4-dinitrophenylhydrazine (86 mg., 1·9 mol.) was refluxed for 18 hr. On cooling, the yellow *bis*-2 : 4-*dinitrophenylhydrazone* separated and was recrystallised from ethanol {yield, 27 mg.; m. p. 104—106°, $[\alpha]_D$ −120° (*c*, 0·50 in $CHCl_3$)} (Found: C, 43·5; H, 4·0; N, 18·9. $C_{21}H_{22}O_{12}N_8$ requires C, 43·6; H, 3·8; N, 19·4%). The "dialdehyde" (V; R = H) after 1 hr. consumed only 0·16 mol. of sodium metaperiodate at pH 4. 1·14 Mol. of sodium hypoiodite was consumed at pH 11·4 in 18 hr. (cf. Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289).

Reduction of Dialdehyde (V; R = H).—Lithium aluminium hydride (0·4 g.) was carefully added to a solution of the dialdehyde (V; R = H) (3·6 g.) in boiling dry ether (250 c.c.), the whole heated under reflux for 15 min., and excess of reagent destroyed by addition of ethyl acetate. Water (500 c.c.) was added, organic solvents were evaporated, and dilute sulphuric acid was added to neutralise the solution. The precipitate was filtered off, and the filtrate evaporated to *ca.* 200 c.c. and then continuously extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated to a syrupy *triol* (VI; R = H) (3·43 g.), $[\alpha]_D$ −35° (*c*, 2·45 in $CHCl_3$) (Found: C, 48·3; H, 8·1. $C_9H_{18}O_6$ requires C, 48·6; H, 8·1%). The triol on oxidation with sodium metaperiodate, buffered ($NaHCO_3$) or unbuffered (*ca.* pH 4), consumed 0·98 mol. of reagent; formic acid could not be detected. Following Bell's method (*J.*, 1948, 992), oxidation of the triol with metaperiodate gave 0·88 mol. of formaldehyde. Acetylation of the triol (132 mg.) in pyridine–acetic anhydride (2 + 0·4 c.c.) for 16 hr. at 20° gave a syrupy *triacetate* (184 mg.), $[\alpha]_D$ −48° (*c*, 3·36 in $CHCl_3$) (Found: C, 52·1; H, 6·9; Ac, 36·5. $C_{15}H_{24}O_9$ requires C, 51·7; H, 6·9; Ac, 37·1%).

L-glycero*Tetrulose* (XI; R = H).—The triol (VI; R = H) (1·01 g.) in 0·05N-sulphuric acid 10 c.c.) was heated at 100° for 1 hr., neutralised ($BaCO_3$), and filtered, and the filtrate extracted continuously with chloroform to remove ethylene glycol. Evaporation of the aqueous solution gave L-*glycero*tetrulose (XI; R = H) as a syrup (350 mg.), $[\alpha]_D$ +7° (*c*, 1·62). Müller, Montigel, and Reichstein (*loc. cit.*) and Whistler and Underköfler (*loc. cit.*) record $[\alpha]_D$ +12°. Iwadare (*loc. cit.*) records $[\alpha]_D^{15}$ −11° for the D-isomer. On the paper chromatogram the syrup gave a yellow-brown spot with R_{Rh} 1·00. L-*glycero*Tetrulose phenylosazone was obtained by treating an aqueous solution (10 c.c.) of the syrup (163 mg.) with phenylhydrazine (0·4 c.c.) and acetic acid (1·5 c.c.) at 50° for 18 hr. The product was filtered off, dried, washed with benzene, and

with water, and recrystallised from aqueous ethanol. The osazone (165 mg.) had m. p. 162°, $[\alpha]_D$ +32° (10 min.) ⟶ 0° (24 hr.; const.) (*c*, 0·75 in C_5H_5N–EtOH, 3 : 2 v/v) (Found: N, 18·6. Calc. for $C_{16}H_{18}O_3N_4$: N, 18·8%).

5-Deoxy-D-threo*pentulose* (VII; R = Me).—The dialdehyde (V; R = H) (713 mg.) was dissolved in boiling dry ether (200 c.c.), and an excess of methylmagnesium iodide [from magnesium (398 mg.) and methyl iodide (1·48 g.) in ether (20 c.c.)] added. After 15 min., water (50 c.c.) was added, and the aqueous layer neutralised with dilute sulphuric acid and filtered, and the filtrate extracted thrice with chloroform (50 c.c.). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to a syrupy 5-deoxypentulose derivative (VI; R = Me) (200 mg.), $[\alpha]_D$ −45° (*c*, 2·00 in $CHCl_3$). On paper chromatograms it gave a single spot (R_F 0·86), yellow with *p*-anisidine hydrochloride and pink with orcinol–trichloroacetic acid (Klevstrand and Nordal, *Acta Chem. Scand.*, 1950, **4**, 1320). The syrup (VI; R = Me) (190 mg.) was hydrolysed with 0·05N-sulphuric acid at 100° for 1 hr. After neutralisation ($BaCO_3$), filtration, and evaporation, paper-chromatographic analysis of the product indicated the presence of 5-deoxy-D-*threo*pentulose (VII; R = Me); propane-1 : 2-diol, expected from the hydrolysis of the 5-deoxypentulose derivative (VI; R = Me), was not detected. Purification of the 5-deoxy-D-*threo*pentulose by chromatography on Whatman No. 1 filter-paper sheets (Flood, Hirst, and Jones, *Nature*, 1947, **160**, 86), followed by elution of the product from the appropriate sections of the filter papers with water, gave syrupy 5-deoxy-D-*threo*pentulose (97 mg.), $[\alpha]_D$ −1° (*c*, 1·94), −15° (*c*, 1·94 in MeOH); Gorin, Hough, and Jones (*J.*, 1953, 2140) record $[\alpha]_D$ −4° (in MeOH). The phenylosazone was prepared by warming the deoxypentulose (48 mg.) in water (5 c.c.) containing phenylhydrazine (0·12 c.c.) and acetic acid (0·5 c.c.) for 6 hr. at 50°. The osazone was filtered off, dried, washed with benzene and water, and recrystallised from aqueous ethanol. The product (15 mg.) had m. p. 171—173°, undepressed on admixture with 5-deoxy-D-*threo*pentose phenylosazone and depressed with 5-deoxy-L-*erythro*pentose phenylosazone. The *X*-ray powder photograph of the product was identical with that of an authentic specimen. Our specimen had $[\alpha]_D$ +73° (10 min.) ⟶ +7° (24 hr., const.) (*c*, 0·55 in C_5H_5N–EtOH, 3 : 2 v/v) (Found: C, 65·4; H, 6·4. Calc. for $C_{17}H_{20}O_2N_4$: C, 65·4; H, 6·4%).

5 : 6-*Dideoxy*-D-threo*hexulose* (VII; R = Et).—The dialdehyde (V; R = H) (700 mg.) was treated with ethylmagnesium bromide as for the foregoing preparation. The 5 : 6-dideoxyhexulose derivative so obtained was a syrup (VI; R = Et) (434 mg.), $[\alpha]_D$ −11° (*c*, 2·17 in $CHCl_3$), which gave on the paper chromatogram a yellow spot with R_F 0·90. The syrup (400 mg.) was hydrolysed as in the preparation of 5-deoxy-D-*threo*pentulose (VII; R = Me) and yielded a product which on paper chromatograms gave a yellow spot (R_{Rh} 2·2; slightly faster than that of 5 : 6-dideoxy-D-*xylo*hexose). Butane-1 : 2-diol was not detected with the ammoniacal silver nitrate spray. Purification by chromatography on Whatman No. 1 filter-paper sheets gave syrupy 5 : 6-dideoxy-D-*threo*hexulose (VII; R = Et) (200 mg.), $[\alpha]_D$ +6° (*c*, 2·50), −8° (*c*, 2·50 in MeOH). The dideoxyhexulose (47 mg.) was dissolved in water (10 c.c.) containing acetic acid (0·5 c.c.), phenylhydrazine (0·12 c.c.) was added, and the solution warmed at 50° for 6 hr. The product was filtered off, dried, washed with benzene, then water, and recrystallised from aqueous ethanol. The osazone (18 mg.) had m. p. 164—165°, undepressed on admixture with 5 : 6-dideoxy-D-*threo*hexose phenylosazone. This gave an *X*-ray powder photograph identical with that of an authentic specimen (see below) and had $[\alpha]_D$ +44° (10 min.) ⟶ +15° (24 hr.; const.) (*c*, 0·55 in C_5H_5N–EtOH, 3 : 2 v/v) (Found: C, 66·6; H, 6·7. Calc. for $C_{18}H_{22}O_3N_4$: C, 66·3; H, 6·7%).

5 : 6-*Dideoxy*-D-xylo*hexose and its Phenylosazone*.—5 : 6-Dideoxy-1 : 2-*O-iso*propylidene-D-*xylo*hexose (McSweeney and Wiggins, *loc. cit.*) (42 mg.) was hydrolysed in 0·1N-sulphuric acid (2 c.c.) at 100° for 1 hr. The solution was neutralised ($BaCO_3$), filtered, and evaporated to a syrup which had $[\alpha]_D$ +2° (*c*, 0·90 in EtOH). Treatment of the aldose (30 mg.) in water (2 c.c.) with phenylhydrazine (0·1 c.c.) and acetic acid (0·3 c.c.) at 80° for 1 hr. gave an *osazone*, which was collected, dried, and washed with benzene and then water. It (13 mg.) had m. p. 167—168° and $[\alpha]_D$ +47° (10 min.) ⟶ +20° (24 hr.; const.) (*c*, 0·60 in C_5H_5N–EtOH, 3 : 2 v/v) (Found: C, 66·1; H, 6·4. $C_{18}H_{22}O_3N_4$ requires C, 66·3; H, 6·7%).

Oxidation of 2 : 3-O-iso*Propylidene*-β-D-*fructopyranose* (XIV) *with Sodium Metaperiodate*.—2 : 3-*O-iso*Propylidene-α-D-fructopyranose (XIV) (860 mg.) in aqueous sodium metaperiodate (4%; 50 c.c.), buffered at pH 6 with 0·7M-potassium dihydrogen phosphate (10 c.c.), was kept for 2 hr. and then continuously extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated to the dialdehyde (XIII; 838 mg.) as a colourless syrup with $[\alpha]_D$ +21° (*c*, 3·35 in $CHCl_3$), which gave on a paper chromatogram a light yellow spot (R_F 0·87). The

syrupy dialdehyde (160 mg.) and 2 : 4-dinitrophenylhydrazine (266 mg., 1·9 mol.) were boiled under reflux in ethanol (50 c.c.) for 20 hr. and, on cooling, the solution yielded yellow crystals which were recrystallised from ethanol to give the *bis*-2 : 4-*dinitrophenylhydrazone* (94 mg.), m. p. 109—113°, $[\alpha]_D$ −10° (*c*, 0·52 in $CHCl_3$) (Found : C, 43·5; H, 3·8. $C_{21}H_{22}O_{12}N_8$ requires C, 43·6; H, 3·8%).

Reduction of the Dialdehyde (XIII).—The dialdehyde (480 mg.) in dry ether (10 c.c.) was added to an excess of lithium aluminium hydride (0·1 g.) in ether (10 c.c.); after 10 min., excess of reagent was destroyed by ethyl acetate. Water (50 c.c.) was then added, organic solvents were evaporated, and the remaining aqueous white sludge was titrated to neutrality with dilute hydrochloric acid. The solution was filtered and extracted continuously with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated to a syrupy triol (XII) (471 mg.), $[\alpha]_D$ +59° (*c*, 3·74 in $CHCl_3$). This gave on a paper chromatogram a light yellow spot (R_F 0·75).

L-glycero*Tetrulose* (XI; R = H).—The triol (XII) (216 mg.) was hydrolysed in 0·1N-sulphuric acid (2 c.c.) at 100° for 1 hr. The solution was neutralised ($BaCO_3$), filtered, and extracted continuously with chloroform to remove ethylene glycol. The aqueous portion was evaporated to a syrup (110 mg.), $[\alpha]_D$ +5° (*c*, 1·7). L-*glycero*Tetrulose (30 mg.) in water (4 c.c.) containing acetic acid (0·5 c.c.) and phenylhydrazine (0·1 c.c.) was kept for 2 hr. at 50°. The osazone was filtered off, dried, washed with benzene, then water, and dried. It had m. p. 160—161° and $[\alpha]_D$ +32° (10 min.) ⟶ 0° (const.; 24 hr.) (*c*, 0·50 in C_5H_5N–EtOH, 3 : 2 v/v) (Found : C, 64·1; H, 6·0; N, 19·2. Calc. for $C_{16}H_{18}O_2N_4$: C, 64·4; H, 6·0; N, 18·8%).

Reaction of the Dialdehyde (XIII) *with Ethylmagnesium Bromide*.—The dialdehyde (549 mg.) in dry ether (10 c.c.) was treated under reflux with excess of ethylmagnesium bromide [prepared from magnesium (800 mg.) and ethyl bromide (2·5 c.c.) in ether (10 c.c.)], then refluxed for 15 min. Water (40 c.c.) was added and the aqueous layer neutralised with dilute sulphuric acid. The solution was filtered and extracted continuously with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated to a syrup (IX) (588 mg.) which had $[\alpha]_D$ +33° (*c*, 5·6 in $CHCl_3$) and gave a yellow spot (R_F 0·90) on a paper chromatogram. The syrup (520 mg.) was hydrolysed with 0·1N-sulphuric acid (5 c.c.) at 100° for 30 min., neutralised ($BaCO_3$), filtered, and evaporated. The syrupy residue gave on a paper chromatogram mainly a yellow-brown spot (R_{Rh} 2·2, corresponding to 5 : 6-dideoxy*threo*hexulose) with traces of *glycero*tetrulose. The product was purified by chromatography on Whatman No. 1 filter-paper sheets to give a syrup (177 mg.), $[\alpha]_D$ −14° (*c*, 2·53 in MeOH), −8° (*c*, 2·53). 5 : 6-Dideoxy-D-*threo*hexulose has $[\alpha]_D$ −8° (*c*, 2·50 in MeOH) and $[\alpha]_D$ +6° (*c*, 2·50). The syrup [(VII) + (X); R = Et] (170 mg.) in water (10 c.c.) containing phenylhydrazine (0·35 c.c.) and acetic acid (2 c.c.) was warmed at 50° for 3 hr. The osazone which separated on cooling was collected, washed with water, and recrystallised from benzene–light petroleum (b. p. 60—80°). The product had a m. p. range 80—110°, indicating a mixture of isomeric phenylosazones (Found : C, 66·3; H, 6·6. Calc. for $C_{18}H_{22}O_3N_4$: C, 66·3; H, 6·7%).

Attempted Preparation of L-glycero*Tetrulose 4-Phosphate* (VII; R = PO_3Ba).—The triol (VIII; R = H) (829 mg.) in pyridine (2·7 c.c.) was treated at 0° with diphenyl phosphorochloridate (2·22 g., 2·2 mol.). After 10 min. at 0° and 18 hr. at 20°, the solution was poured into aqueous sodium hydrogen carbonate (50 c.c.), and the solution extracted twice with equal volumes of chloroform. The combined extract was shaken with water, dried ($MgSO_4$), filtered, and evaporated to a syrup [VIII; R = $PO(OPh)_2$] (2·58 g.), $[\alpha]_D$ −14° (*c*, 2·18 in MeOH) (Found : P, 8·8. $C_{35}H_{36}O_{12}P_2$ requires P, 9·0%). The *bis*(*diphenyl phosphate*) [VIII; R = $PO(OPh)_2$] (871 mg.) was boiled under reflux in methanol (20 c.c.) containing activated charcoal (0·5 g.) for 10 min. to remove catalyst poisons. The solution was filtered and made up to 50 c.c. with methanol. Water (16 c.c.), barium carbonate (2 g.), and Adams catalyst (150 mg.) were added and the mixture was shaken in hydrogen at 1 atm. After 4 hr., when uptake of hydrogen had ceased, the solution was filtered and evaporated to a white solid (VIII; R = PO_3Ba) (697 mg.), $[\alpha]_D$ −15° (*c*, 0·57).

In order to find suitable conditions for hydrolysis of the *iso*propylidene groups and not the phosphate, a portion (32·6 mg.) was dissolved in 0·1N-sulphuric acid (30 c.c.), barium sulphate was centrifuged off, and the residue heated at 80°. At intervals samples were taken and the amount of inorganic phosphate liberated estimated by the method of Foster, Overend, and Stacey (*loc. cit.*). After 4 hr., 8% of the total phosphate was liberated. The salt (VIII; R = PO_3Ba) (138 mg.) was partially hydrolysed in 0·1N-sulphuric acid (15 c.c.) at 80° for 4 hr. It was titrated to pH 7 with aqueous barium hydroxide, the solution filtered, and the filtrate evaporated to a small volume. An excess of acetone was added and the precipitated material collected, triturated with ethanol, and recovered. The product (23 mg.) was examined on

paper chromatograms (Whatman No. 542; ethyl acetate–acetic acid–formic acid–water, 18 : 3 : 1 : 4 v/v). The presence of two compounds was indicated. The slower-moving material (R_{Gal} 0·74) (L-*glycero*tetrulose 4-phosphate ?) gave a blue colour with the ammonium molybdate–perchloric acid phosphate spray (Hanes and Isherwood, *Nature*, **1949**, **164**, 1107) and a yellow colour with the *p*-anisidine hydrochloride spray. The faster-moving material (2-hydroxyethyl dihydrogen phosphate ?) gave a blue spot (R_{Gal} 1·3) with the phosphate spray and no colour with the *p*-anisidine hydrochloride spray. The original compound (VIII; R = PO_3Ba) which gave yellow and blue spots (R_{Ith} 1·2) with the *p*-anisidine hydrochloride and phosphate sprays respectively, was not present.

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The Synthesis and Reactions of Branched-chain Hydrocarbons. Part IX. The Preparation of some Branched-chain Alcohols and Ketones.*

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The preparation of some branched-chain alcohols and ketones by the Grignard reaction from acid chlorides and acid anhydrides is described.

FOR other investigations it was necessary to prepare the substituted dialkyl ketones (I) and (II), and the corresponding alcohols, in quantity and in a high degree of purity.

$Bu^t{\cdot}CO{\cdot}R$ [I; R = (*a*) Et, (*b*) Pr^i, (*c*) Bu^t]

$CMe_2Et{\cdot}CO{\cdot}R$ [II; R = (*a*) Me, (*b*) Et, (*c*) CH_2Bu^t]

2 : 2-Dimethylpentan-3-one (I*a*) and 3 : 3-dimethylpentan-2-one (II*a*) were prepared by the interaction of the appropriate Grignard reagent and acid anhydride at −70° (cf. Newman and Smith, *J. Org. Chem.*, **1948**, **13**, 592). This appears to be a more convenient and satisfactory method than that described by Whitmore *et al.* (*J. Amer. Chem. Soc.*, **1939**, **61**, 683; **1942**, **64**, 2964). In the preparation of 4 : 4-dimethylhexan-3-one (II*b*) from *tert.*-pentylmagnesium chloride and propionic anhydride the yield of ketone was reduced by concurrent formation of *n*-propyl propionate. Use of this method to obtain the more highly substituted ketone, 2 : 2 : 4-trimethylpentan-3-one (I*b*), was even less successful. A better approach to the remaining ketones (I*b*, I*c*, and II*c*) was found in the reaction between the appropriate acid chloride and Grignard reagent in the presence of cuprous chloride or copper (Cook *et al.*, *ibid.*, 1949, **71**, 1509, 4141). Thus 2 : 2 : 5 : 5-tetramethylheptan-4-one (II*c*) was prepared from *tert.*-pentylmagnesium chloride and 3 : 3-dimethylbutanoyl chloride; † 3 : 3-dimethylbutan-1-ol and its ester with 3 : 3-dimethylbutanoic acid were also formed. 2 : 2 : 4-Trimethylpentan-3-one (I*b*) was similarly prepared from pivaloyl chloride and *iso*propylmagnesium chloride, and although the yield was only moderate the method was more convenient for the large-scale preparation of the pure ketone than the methylation of 2 : 4-dimethylpentan-3-one (Whitmore and Stahley, *ibid.*, **1933**, **55**, 4155). Attempts to prepare 2 : 2 : 4-trimethylhexan-3-one (I*c*) by addition of *sec.*-butylmagnesium chloride to pivaloyl chloride gave an inseparable

* Part VIII, *J.*, 1955, 1781. † Geneva nomenclature, CO_2H = 1.

mixture of the required ketone, *neo*pentyl alcohol, and *neo*pentyl pivalate. Reversal of the order of mixing the reagents gave, even in the presence of cuprous chloride, mainly *neo*pentyl alcohol. The ketone was eventually obtained by the oxidation of 2 : 2 : 4-trimethylhexan-3-ol, which was prepared in good yield by adding α-methylbutyryl chloride to an excess of *tert.*-butylmagnesium chloride.

Experimental

Reaction of Grignard Reagents with Acid Anhydrides.—A filtered solution of the Grignard reagent, prepared from the alkyl halide (5·0 mole), magnesium (121·6 g.), and ether (1200 c.c.) by Whitmore and Badertscher's method (*J. Amer. Chem. Soc.*, 1933, **55**, 1559), was added during 12 hr. to a stirred solution of the acid anhydride (5·0 mole) in ether (300 c.c.) and the mixture was kept at −70°. Stirring was continued for a further 2 hr., and the mixture allowed to warm to 0° and then decomposed by the dropwise addition of a solution of ammonium chloride (321 g.) in water (2 l.). The ethereal layer was separated, the aqueous layer was extracted with ether (3 × 200 c.c.), and the combined ethereal solutions were washed with 10% aqueous sodium hydroxide (2 × 600 c.c.) and water. The washings were extracted with ether (3 × 100 c.c.). After being dried (Na_2SO_4), the ether was removed from the combined ethereal solutions, and the residue fractionally distilled through a 50-cm. column packed with Dixon gauze. In this way were prepared: (*a*) From *tert.*-butyl chloride and propionic anhydride, 2 : 2-dimethylpentan-3-one (269 g.), b. p. 125—126°, n_D^{20} 1·4050 [2 : 4-dinitrophenylhydrazone, orange (from aqueous alcohol), m. p. 174—175°]; Whitmore, Noll, and Meunier (*ibid.*, 1939, **61**, 683) record b. p. 124·5°/729 mm., n_D^{20} 1·4049—1·4052. Kharasch, Sternfeld, and Mayo (*J. Org. Chem.*, 1940, **5**, 362) give 2 : 4-dinitrophenylhydrazone, m. p. 175°. (*b*) From *tert.*-pentyl chloride and acetic anhydride, 3 : 3-dimethylpentan-2-one (175 g.), b. p. 131—132°, n_D^{20} 1·4098—1·4100 [2 : 4-dinitrophenylhydrazone, yellow felted needles (from aqueous alcohol), m. p. 112°]; Whitmore and Lewis (*J. Amer. Chem. Soc.*, 1942, **64**, 2964) record b. p. 130°/733 mm., n_D^{20} 1·4100, and 2 : 4-dinitrophenylhydrazone, m. p. 112°. (*c*) From *tert.*-pentyl chloride and propionic anhydride, *n*-propyl propionate (37·8 g.), b. p. 122—124°, n_D^{20} 1·3936 [Tischtschenko (*Chem. Zentr.*, 1906, II, 1552) records b. p. 122—124°], and 4 : 4-dimethylhexan-3-one (105 g.), b. p. 150·5—151·5°, n_D^{20} 1·4163—1·4165 [2 : 4-*dinitrophenylhydrazone*, yellow needles (from aqueous alcohol), m. p. 86° (Found: C, 54·7; H, 6·6; N, 17·9. $C_{14}H_{20}O_4N_4$ requires C, 54·5; H, 6·5; N, 18·2%), semicarbazone, white plates (from light petroleum, b. p. 60—80°), m. p. 97—98°]. Parry (*J.*, 1915, **110**) records b. p. 150—152°, and semicarbazone, m. p. 97—98°. (*d*) From *iso*propyl bromide and pivalic anhydride (see below) (on 0·2-mole scale), a fraction (2·4 g.), b. p. 60—130°, containing pivalaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 208°) and 2 : 2 : 4-trimethylpentan-3-one (3·9 g.), b. p. 132°, characterised by reduction with lithium aluminium hydride to 2 : 2 : 4-trimethylpentan-3-ol (3 : 5-dinitrobenzoate m. p. and mixed m. p. 104—106°).

Pivalic Anhydride.—A mixture of pivalic acid (50 g.) and acetic anhydride (90 g.) was slowly distilled through a 12" helix-packed column at such a rate that the vapour temperature at the top of the column did not exceed 120°. When the temperature rose above 120°, acetic anhydride (10 c.c.) was added and the above procedure repeated. Fractional distillation of the residue through an efficient column gave pivalic anhydride (35·7 g.), b. p. 78°/12 mm., n_D^{20} 1·4089 [Butlerow (*Annalen*, 1874, **173**, 374) records b. p. 190°]. On treatment with aniline, only pivalanilide, m. p. and mixed m. p. 134°, was formed [Found: *M* (by hydrolysis), 181·2. Calc. for $C_{10}H_{13}O_2$: *M*, 186].

2 : 2 : 4-*Trimethylpentan*-3-*one.*—A filtered solution of the Grignard reagent prepared from *iso*propyl chloride (392 g., 5 mole) and magnesium (120 g., 5 g.-atom) in ether (1 l.) was added during 4 hr. to a well-cooled (ice-salt) stirred mixture of pivaloyl chloride (622 g., 5 mole) cuprous chloride (7 g.), copper powder (1 g.), and ether (1·5 l.). Stirring was continued overnight, while the mixture warmed to room temperature. It was then poured on crushed ice (1·5 kg.) and concentrated hydrochloric acid (550 c.c.), the ethereal layer separated, and the aqueous layer extracted with ether. The combined ethereal solutions were washed with 5% sodium hydroxide solution (4 × 250 c.c.), then dried ($CaCl_2$), and ether removed through a 60-cm. column packed with single turn Fenske helices. The products from two such preparations were combined and fractionally distilled through a 60-cm. column packed with Dixon gauzes to yield a mixture (9·3 g.), b. p. >60°/88 mm., of pivalaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 210—211°) and *iso*propyl alcohol (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 122°);

2 : 2 : 4-trimethylpentan-3-one (456 g.), b. p. 61·5—63°/79 mm., n_D^{20} 1·4030—1·4054 (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 166—167°); and a non-homogenous fraction (272 g.), b. p. 83—104°/77 mm., containing *neo*pentyl pivalate (identified by hydrolysis to pivalic acid and *neo*pentyl alcohol) and 2 : 4 : 4-trimethylpentan-3-ol (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 105—106°).

2 : 2 : 5 : 5-*Tetramethylheptan*-4-*one*.—A filtered solution of the Grignard reagent prepared from *tert*.-pentyl chloride (106 g., 1 mole) and magnesium (24 g.) in ether (300 c.c.) was added during 2 hr. to a well-cooled (ice-salt) stirred (copper stirrer) mixture of cuprous chloride (1 g.) and 3 : 3-dimethylbutanoyl chloride (96 g.) in ether (500 c.c.). The subsequent procedure was as described above. Fractional distillation of the residue obtained after removal of the ether gave: (*a*) A mixture (4·3 g.) of unsaturated material and 3 : 3-dimethylbutan-1-ol, b. p. 30°/14 mm. (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 83·5°). (*b*) 2 : 2 : 5 : 5-*Tetramethylheptan*-4-*one* (46·3 g.), b. p. 60—70°/14 mm., n_D^{20} 1·4240—1·4242 (b. p. 70°/14 mm., n_D^{20} 1·4242 on analytical sample) (Found: C, 77·9; H, 12·9. $C_{11}H_{22}O$ requires C, 77·5; H, 13·0%). No carbonyl derivative could be obtained. Reduction of the ketone with lithium aluminium hydride gave 2 : 2 : 5 : 5-*tetramethylheptan*-4-*ol*, b. p. 83°/14 mm., n_D^{20} 1·4406 (Found: C, 76·7; H, 14·0. $C_{11}H_{24}O$ requires C, 76·6; H, 14·0%) {3 : 5-*dinitrobenzoate* [from light petroleum (b. p. 40—60°)], m. p. 108° (Found: C, 59·0; H, 7·1; N, 7·6. $C_{18}H_{26}O_6N_2$ requires C, 59·0; H, 7·1; N, 7·7%)} (cf. Ansell, Hickinbottom, and Hyatt, *J.*, 1955, 1592). (*c*) A fraction (16·1 g.), b. p. 70—75°/14 mm., which on redistillation gave the above ketone and 3 : 3-dimethylbutyl 3 : 3-dimethylbutanoate (8·3 g.), b. p. 94°/17 mm., m. p. and mixed m. p. 22° (cf. Whitmore Mattil and Popkin, *J. Amer. Chem. Soc.*, 1938, **60**, 2790).

2 : 2 : 4-*Trimethylhexan*-3-*one and* 2 : 2 : 4-*Trimethylhexan*-3-*ol*.—(*a*) A filtered solution of the Grignard reagent prepared from *sec*.-butyl chloride (92 g., 1 mole) and magnesium (24·3 g., 1 g.-atom) in ether (220 c.c.) was added during 1½ hr. to a well-cooled (ice-salt) mixture of pivaloyl chloride (120 g., 1 mole), cuprous chloride (3 g.), and copper powder (10 g.) in ether (400 c.c.). The subsequent procedure was as in the previous examples. Fractional distillation of the residue obtained after removal of the ether gave: a fraction, b. p. <38°, containing pivalaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 210—211°); a fraction, b. p. 87—90°/80 mm., containing *neo*pentyl alcohol (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 90—91°), 2 : 2 : 4-trimethylhexan-3-one [2 : 4-*dinitrophenylhydrazone*, yellow needles (from aqueous alcohol), m. p. 130—130·5° (Found: C, 55·6; H, 7·0; N, 17·2. $C_{15}H_{22}O_4N_4$ requires C, 55·9; H, 6·9; N, 17·4%)], and *neo*pentyl pivalate (identified by the formation of pivalic acid on hydrolysis).

(*b*) Pivaloyl chloride (120 g., 1 mole) was added during 5 hr. to a stirred, filtered solution of the Grignard reagent prepared from *sec*.-butyl chloride (276 g., 3 mole) and magnesium (72 g., 3 g.-atom) in ether (1·2 l.). It was then poured on a mixture of ice and sulphuric acid. The subsequent procedure was as in the previous examples. Fractional distillation of the residue obtained on removal of the ether from the dried ($MgSO_4$) ethereal extracts gave, after a small fore-run, *neo*pentyl alcohol (56 g.), b. p. 114—116° (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 91°.

(*c*) α-Methylbutyryl chloride (348 g., 2·9 mole) was added during 5 hr. to a stirred, filtered solution of the Grignard reagent prepared from *tert*.-butyl chloride (883 g., 9·6 mole) and magnesium (234 g., 9·6 g.-atom) in ether (3·7 l.). The subsequent procedure was as in (*b*). The distillate from three combined runs gave *tert*.-butyl alcohol (80 g.), b. p. 76—80° (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 141—142°), 2-methylbutan-1-ol (20 g.), b. p. 126—128° (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 68—69°), and 2 : 2 : 4-trimethylhexan-3-ol (672 g.), b. p. 171—172° [phenylurethane, m. p. 78—80° [Haller and Bauer (*Compt. rend.*, 1910, **150**, 582) record m. p. 78°]. Oxidation of the alcohol with chromium trioxide in acetic acid gave 2 : 2 : 4-trimethylhexan-3-one, isolated as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 130°.

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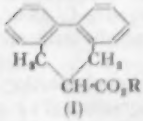
The Relation between Configuration and Conjugation in Diphenyl Derivatives. Part V. 2 : 2′-Bridged Compounds with Seven- and Eight-membered Homocyclic Rings.*

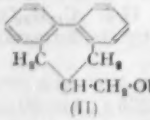
By G. H. Beaven, Gwendoline R. Bird, D. Muriel Hall, E. A. Johnson, Joan E. Ladbury, Mary S. Lesslie, and E. E. Turner.

[Reprint Order No. 6298.]

2 : 2′-Bisbromomethyldiphenyl has been condensed with the sodio-derivatives of ethyl malonate and ethyl ethane-1 : 1 : 2 : 2-tetracarboxylate. Hydrolysis of the esters produced, followed by decarboxylation, gave 3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylic acid and two isomeric 4 : 5-6 : 7-dibenzo*cyclo*octa-4 : 6-diene-1 : 2-dicarboxylic acids respectively. The ultraviolet absorption spectra of the methyl esters of these acids are discussed in relation to their configurations. The condensation of the dibromide with ethyl propane-1 : 1 : 3 : 3-tetracarboxylate led to scission of the aliphatic ester and the formation of ethyl 3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1 : 1-dicarboxylate.

The reaction between 2 : 2′-bisbromomethyldiphenyl and sodiomalonic ester produces ethyl 3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1 : 1-dicarboxylate (Kenner, *J.*, 1913, **103**, 613), from which 3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylic acid (I; R = H) may be obtained. By the use of sodio-derivatives of other esters it was hoped to synthesise similar acids in which the 2 : 2′-bridge would form part of an eight- or nine-membered or even larger ring. In such compounds the increased size of the bridging ring may be expected to lead to greater twisting of the two benzene rings about the common axis with consequent further reduction in conjugation between them, detectable by changes in the ultraviolet absorption spectra.


(I)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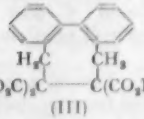
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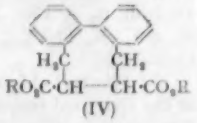

(IV)

We have succeeded in preparing the compounds containing an eight-membered bridging ring but not those with the larger rings.

3 : 4-5 : 6-Dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylic acid (I; R = H) was prepared by Kenner's method. The absorption spectra of the acid, of its methyl ester (I; R = Me; Fig. 1) and of 1-hydroxymethyl-3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene (II) in 96% ethanol are all of the simple diphenyl type, with the conjugation band at the same wavelength as in diphenyl itself (249 mμ) but of slightly reduced intensity (*ca.* 15,000 instead of 17,000). The long-wave features in the spectra of these three compounds are barely discernible inflections; their apparent molecular extinctions are irrelevant because of heavy overlapping by the strong conjugation bands, and the actual contributions from the phenyl partial chromophores must be very small. The small reduction in conjugation compared with diphenyl is thus practically the same as that observed with the seven-membered bridged heterocyclic compound, 2 : 7-dihydro-3 : 4-5 : 6-dibenzoxepin (Part I; Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854).

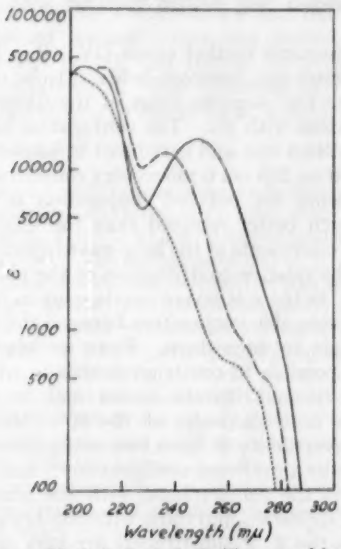
The angle between the ring planes in the 3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene structure according to a model is about 50°; direct calculation (using 1·54 Å for the $C_{(1)}$–$C_{(2)}$ and $C_{(2)}$–$C_{(3)}$ bonds and 1·40 Å for the $C_{(3)}$–$C_{(4)}$ bond) gives a value of 48·6° if the $C_{(4)}$–$C_{(5)}$ bond is 1·53 Å and 49·1° if the $C_{(4)}$–$C_{(5)}$ bond is 1·50 Å.

All attempts to effect the optical resolution of the acid (I; R = H) or the alcohol (II) failed (cf. Bell, *J.*, 1952, 1527). The brucine, quinine, and strychnine salts of the acid were

* Part IV, *J.*, 1954, 2552.

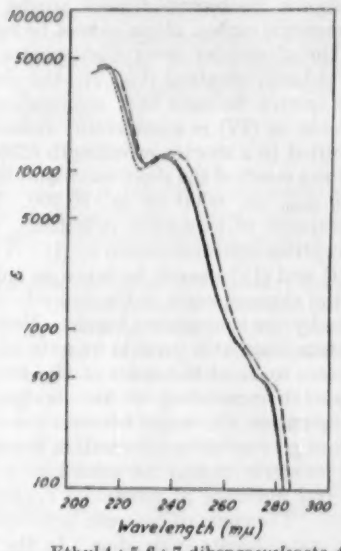
investigated in various solvents and also the (−)-menthyl and (−)-cholesteryl esters. The (−)-menthoxyacetate and the brucine salt of the hydrogen phthalate of the alcohol were studied. Decarboxylation of the dibrucine salt of 3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1 : 1-dicarboxylic acid yielded optically inactive monocarboxylic acid. The quinine salt of (I) showed a rather unusual feature in that the quinine behaved as a diacidic base, even when the salt was prepared in ethanol starting with *equimolecular* proportions of acid and alkaloid. The (1 : 1)-salt was obtained from an acetone–light petroleum solution, but on

FIG. 1.



——— Methyl 3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylate (I; R = Me).
– – – – Methyl 4 : 5-6 : 7-dibenzo*cyclo*octa-4 : 6-diene-1 : 2-dicarboxylate (IV; R = Me), m. p. 139—141°.
– – – – 2 : 2′-Di-(2-methoxycarbonyl-*n*-propyl)-diphenyl.

FIG. 2.



– – – – Ethyl 4 : 5-6 : 7-dibenzo*cyclo*octa-4 : 6-diene-1 : 1 : 2 : 2-tetracarboxylate (III).
——— Methyl 4 : 5-6 : 7-dibenzo*cyclo*octa-4 : 6-diene-1 : 2-dicarboxylate (IV; R = Me), m. p. 126·5—128°.
– – – – – Methyl 4 : 5-6 : 7-dibenzo*cyclo*octa-4 : 6-diene-1 : 2-dicarboxylate (IV; R = Me), m. p. 139—141°.

crystallisation from ethanol gave the (2 : 1)-salt together with a gel which was mainly quinine. The methyl ester (I; R = Me) was examined for unstable optical activity by dissolution in diethyl (+)-tartrate (Buchanan and Graham, *J.*, 1950, 500; Glazer, Harris, and Turner, *ibid.*, p. 1753) with negative results. Further, the acid itself failed to undergo first-order asymmetric transformation in the presence of brucine in chloroform solution.

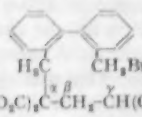
Kenner (*loc. cit.*) condensed 2 : 2′-bisbromomethyldiphenyl with ethyl ethane-1 : 1 : 2 : 2-tetracarboxylate in the presence of sodium ethoxide in ethanol at 120—140° under pressure for 5 hours and obtained a crystalline ester, m. p. 108·5°, with the correct analysis for the expected product (III) but with a low molecular weight as determined cryoscopically in benzene solution. We have obtained the same compound by adding the dibromide in ethereal solution to the sodio-ester in ethanol and then distilling off the ether during 3 hours; the solution then had a " neutral " reaction. The molecular weight of the ester as observed in undried benzene was a little low but as determined ebullioscopically in benzene solution by Menzies and Wright's method (*J. Amer. Chem. Soc.*, 1921, **43**, 2314) was correct.

The absorption spectrum of the ester (III) (Fig. 2) is very similar to the spectra of the corresponding dicarboxylic esters (IV; R = Me) discussed below, except for a general small shift (2—4 mμ) to longer wavelengths.

Alkaline hydrolysis in 2-ethoxyethanol was accompanied by decarboxylation, giving a dicarboxylic acid (IV; R = H), m. p. *ca.* 235° (decomp.). When this was heated at 250—260° it passed partly into an anhydride, which on dissolution in potassium hydroxide, followed by acidification with cold acid, gave a second dicarboxylic acid, obtained as a partial hydrate, m. p. *ca.* 202° (decomp.). The two acids gave rise to two series of esters, those from the second acid having the higher melting points. It was not found possible to obtain a pure anhydride from the first acid. The most probable explanation of the two series of compounds is that they are *cis* and *trans* isomers, although the possibility of additional diastereoisomerism arising from the twisted ring system together with the asymmetric carbon atoms cannot be ruled out.

The ultraviolet absorption spectra of the two isomeric methyl esters (IV; R = Me) are virtually identical (Fig. 2); the observed differences are, however, believed to be real. The spectra indicate that conjugation between the two benzene rings of the diphenyl skeleton in (IV) is considerably reduced in comparison with (I). The conjugation band is shifted to a shorter wavelength (236·5 instead of 248·5 mμ) and is reduced in intensity; and as a result of the short-wave shift the minimum at *ca.* 228 mμ is raised very considerably from $\varepsilon_{min.}$ *ca.* 6000 to *ca.* 10,500. Further evidence for reduced conjugation is the appearance of long-wave inflections, which are much better resolved than the scarcely perceptible inflection shown by (I). The extinction coefficients at the long-wave inflections in (I) and (IV) cannot be taken as indications of the relative contributions of the phenyl partial chromophores in the two sets of compounds, as there is severe overlapping in both cases by the conjugation bands. Nevertheless, considerable conjugation between the two benzene rings still persists in spite of the large angle between them. From models this appears to be of the order of 60—65°. It is also possible to construct models in which greater overcrowding of the bridging ring and its substituents occurs and in this configuration the angle between the benzene rings is of the order of 75—80°. Models cannot give accurate information about the interconvertibility of these two configurations, but for steric reasons the second one is not likely to be a preferred configuration; and the spectral evidence of remaining conjugation favours the configuration with the smaller angle. The contrast between non-coplanar bridged diphenyls and those with non-bridging 2 : 2′-substituents is striking. In the latter, unless the 2 : 2′-substituents are very small (*e.g.*, fluorine, cf. Part VI) conjugation is very greatly reduced and the long-wave features are much more evident (cf. 2 : 2′-ditolyl, Part III, Beaven, Hall, Lesslie, Turner, and Bird, *J.*, 1954, 131), even though transient coplanarity (in the "*trans*" position) can undoubtedly be achieved.

The interaction of 2 : 2′-bisbromomethyldiphenyl and ethyl propane-1 : 1 : 3 : 3-tetracarboxylate in the presence of sodium ethoxide failed to give the expected compound with a nine-membered bridging ring. Instead, fission of the carbon chain of the ester occurred and ethyl 3 : 4-5 : 6-dibenz*oc*yclohepta-3 : 5-diene-1 : 1-dicarboxylate was produced in about 60% yield. Hydrolysis and decarboxylation led to 3 : 4-5 : 6-dibenz*oc*yclohepta-3 : 5-diene-1-carboxylic acid (I; R = H), identified by mixed melting points, the absorption spectrum, and the molecular weight of its methyl ester. It seems likely that initially a singly charged anion of the ester is produced and reacts normally with one bromomethyl group, giving (V). In the second stage the other bromomethyl group is attacked by the α-carbon atom rather than the γ-carbon atom, even though the latter can acquire a negative charge (in the presence of ethoxide ions). Such behaviour by this ester is not unknown. Guthzeit and Engelmann (*J. prakt. Chem.*, 1902, **66**, 104) found that it reacted with two molecules of ethyl bromoacetate in the presence of sodium ethoxide to give a mixture of the normal product, ethyl pentane-1 : 2 : 2 : 4 : 4 : 5-hexacarboxylate (VI) (attack in stage 2 by the γ-carbon atom), and ethyl propane-1 : 2 : 2 : 3-tetracarboxylate (VII) (attack in stage 2 by the α-carbon atom), the proportions varying with the experimental conditions and the yields being rather low. In the case of compound (V) attack by the α-carbon atom is strongly favoured sterically and although evidence of the product of attack by the γ-carbon atom was specifically looked for it was not obtained.

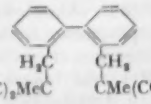


(V)

The strong tendency for the formation of the seven-membered ring is further shown by Kenner's observation (*loc. cit.*) that in the condensation between the dibromide and sodiomalonic ester, the use of two molecular proportions of malonic ester still leads to the same

$EtO_2C{\cdot}CH_2{\cdot}C(CO_2Et)_2{\cdot}CH_2{\cdot}C(CO_2Et)_2{\cdot}CH_2{\cdot}CO_2Et$
(VI)

$EtO_2C{\cdot}CH_2{\cdot}C(CO_2Et)_2{\cdot}CH_2{\cdot}CO_2Et$
(VII)


(VIII)

cyclic product; whereas we find that with two molecular proportions of ethyl methylmalonate normal interaction occurs, giving 2 : 2′-di-(2 : 2-diethoxycarbonyl-*n*-propyl)-diphenyl (VIII), and thence, by hydrolysis and decarboxylation, 2 : 2′-di-(2-carboxy-*n*-propyl)diphenyl. The spectrum of the dimethyl ester of this acid (Fig. 1) has the characteristics expected for an unbridged 2 : 2′-dialkyldiphenyl.

Experimental

3 : 4-5 : 6-Dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylic acid, m. p. 161—162°, was prepared by Kenner's method (*loc. cit.*) from 2 : 2′-bisbromomethyldiphenyl (Hall, Lesslie, and Turner, *J.*, 1950, 711) *via* **3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1 : 1-dicarboxylic acid**, m. p. *ca.* 218° (decomp.). The methyl ester had m. p. 46—47°.

Attempted Resolution.—(a) *Quinine salt.* The *neutral* salt was made by dissolving the acid (2·4 g., 2 mols.) and quinine dihydrate (1·8 g., 1 mol.) in ethanol (20 c.c.). The salt (3·1 g.) which separated was air-dried; it had $[\alpha]_{5791}$ −69·7°, $[\alpha]_{5461}$ −80·9° (*c*, 2·699 in $CHCl_3$) (Found: C, 76·5; H, 7·1. $C_{29}H_{34}O_8N_2,2C_{16}H_{14}O_2,C_2H_6O$ requires C, 76·6; H, 6·9%). An identical salt ($[\alpha]_{5791}$ −69·6°, $[\alpha]_{5461}$ −80·7°) was obtained by dissolving equimolecular amounts of acid and quinine dihydrate in ethanol. In this case evaporation of the solvent from the mother-liquor gave a glass which was mainly quinine. The basic salt was obtained by dissolving equimolecular amounts of the acid and anhydrous quinine in acetone and adding light petroleum (b. p. 60—80°). This salt had $[\alpha]_{5791}$ −89·8°, $[\alpha]_{5461}$ −104·2° (in $CHCl_3$); a chloroform solution made up to contain equimolecular amounts of the acid and quinine had $[\alpha]_{5791}$ −89·0°, $[\alpha]_{5461}$ −102·8°. Crystallisation of this salt from ethanol gave the neutral salt, $[\alpha]_{5791}$ −69·5°, $[\alpha]_{5461}$ −81·0°, and a gel which was mainly quinine.

(b) *Cholesteryl ester.* The acid chloride was prepared by using thionyl chloride and was obtained as a solid, m. p. 72—74° after crystallisation from light petroleum (b. p. 40—60°) (cf. Kenner, *loc. cit.*). The chloride (8 g.), dissolved in benzene (20 c.c.), was added to cholesterol (10·8 g.), dissolved in pyridine (50 c.c.), and the mixture warmed to 50°. After 3 hr. dilute hydrochloric acid was added; the benzene solution was separated and washed, and the solvent removed. The crude ester (14·5 g.) was crystallised from acetone and had m. p. 105—107°, $[\alpha]_{5791}$ −20·6°, $[\alpha]_{5461}$ −23·9° (*c*, 2·426 in $CHCl_3$) (Found: C, 85·1; H, 9·95. $C_{43}H_{66}O_2$ requires C, 85·1; H, 9·6%). The specific rotation was unchanged by further recrystallisation.

1-*Hydroxymethyl*-3 : 4-5 : 6-*dibenzo*cyclo*hepta*-3 : 5-*diene* (II).—The *alcohol* was prepared by the reduction of methyl **3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylate** with lithium aluminium hydride in ethereal solution. It crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 131·5° (Found: C, 85·5; H, 7·2. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1%). The *hydrogen phthalate*, crystallised from aqueous acetic acid, had m. p. 145° (Found: C, 77·1; H, 5·4. $C_{24}H_{20}O_4$ requires C, 77·4; H, 5·4%). A brucine salt of the hydrogen phthalate was made but its specific rotation was unaltered by repeated crystallisation, and decomposition gave the inactive hydrogen phthalate. The (−)-*menthoxyacetate* was made by the usual method in pyridine solution. It crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 62—63° (Found: C, 80·2; H, 8·3. $C_{28}H_{36}O_3$ requires C, 80·0; H, 8·6%). The specific rotation varied slightly on recrystallisation but no clear separation into two esters occurred.

Ethyl **4 : 5-6 : 7-*Dibenzo*cyclo*octa*-4 : 6-*diene*-1 : 1 : 2 : 2-*tetracarboxylate***.—Sodium (4·1 g., 2 atom-equivs.) was dissolved in absolute ethanol (85 c.c.), and ethyl ethane-1 : 1 : 2 : 2-tetracarboxylate (28 g., 1 mol.) added (as solid) with stirring, followed immediately by the dibromide (30 g., 1 mol.) in ethereal solution (250 c.c.). The mixture was heated under reflux for 1 hr. and then the ether distilled off during 3 hr. The solution then had a neutral reaction. Water was added and the solid ester so obtained was washed with light petroleum and crystallised from *n*-hexane, giving 23 g. (52%), m. p. 107—109°. Recrystallisation raised the m. p. to 108—109·5°

[Found: C, 67·7; H, 6·2%; *M* (cryoscopic in undried benzene) 455, (in *cyclo*hexane) 456; (ebullioscopic in benzene) 502, 501. Calc. for $C_{28}H_{32}O_6$: C, 67·7; H, 6·5%; *M*, 496].

4 : 5-6 : 7-*Dibenzo*cyclo*octa*-4 : 6-*diene*-1 : 2-*dicarboxylic Acids*.—*Hydrolysis of the tetraethyl ester.* (*a*) The ester was boiled under reflux with ethanolic potassium hydroxide for 6 hr. and water then added. About half the ester was recovered unchanged. This was then treated with ethanolic potassium hydroxide for another 15 hr. The acid so obtained (from both parts of the hydrolysis) was crystallised from aqueous ethanol and had m. p. *ca.* 230° (decomp.).

(*b*) The ester was boiled under reflux for 6 hr. with potassium hydroxide dissolved in 2-ethoxyethanol containing a little water. A large volume of water was added, the solution extracted with ether, and hydrochloric acid added. The acid was crystallised from aqueous alcohol and had m. p. *ca.* 235° (decomp.). Analysis showed it to be the *dicarboxylic acid* (Found: C, 72·6; H, 5·6. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). The yield was 81%.

Some of this acid (6·0 g.) was heated at 250° and it decomposed with loss of water (it was at this time supposed to be the tetracarboxylic acid). The residue was dissolved in hot ethanol and the solution deposited an *anhydride* (1·65 g.) which, after recrystallisation from *cyclo*hexane, had m. p. 173—174° (Found: C, 77·5; H, 5·2. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·1%).

The anhydride was dissolved in hot aqueous potassium hydroxide and the acid precipitated from the cooled solution. This acid crystallised from aqueous ethanol and had m. p. *ca.* 202° (decomp.). It appeared to be partially (and variably) hydrated (Found: C, 71·3, 72·4, 70·8; H, 6·2, 5·7, 5·5. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4. $C_{18}H_{16}O_4.H_2O$ requires C, 68·8; H, 5·8%). It could be reconverted into the anhydride by the action of boiling acetic anhydride. The *dimethyl ester* was prepared from the anhydride and crystallised from methanol in long prisms, m. p. 139—141° (Found: C, 74·2; H, 6·4. $C_{20}H_{20}O_4$ requires C, 74·05; H, 6·2%). The *diethyl ester*, crystallised from ethanol, had m. p. 77—78·5° (Found: C, 75·2; H, 7·0. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·9%).

Esters were prepared from the isomeric acid, m. p. 235° (decomp.). The *dimethyl ester* had m. p. 126·5—128° (Found: C, 74·0; H, 6·4%). The *diethyl ester* had m. p. 58·5—60° (Found: C, 74·9; H, 7·05%). Attempts to prepare the anhydride of this acid were unsuccessful.

The ethanolic mother-liquor, after separation of the anhydride, was concentrated, but no more solid was obtained, presumably owing to reaction of the anhydride with ethanol to give the half-ester. The ethanolic solution was therefore heated with alcoholic potassium hydroxide, and acid (3·4 g.) recovered from it. This was a mixture of the two acids and, although separation was difficult, a little of each acid was isolated from it.

Reaction of **2 : 2′-*Bisbromomethyldiphenyl with Ethyl Propane*-1 : 1 : 3 : 3-*tetracarboxylate*.**—The ester (*Org. Synth.*, Coll. Vol. I, 2nd edn., p. 290) was fractionated four times under reduced pressure. Sodium (3·45 g., 2 atom-equivs.) was dissolved in absolute ethanol (60 c.c.), and the ester (24·9 g., 1 mol.) added with stirring, followed by the dibromide (25·5 g., 1 mol.), which had been finely ground and dissolved in the minimum amount of dry ether (*ca.* 220 c.c.). Immediate separation of sodium bromide occurred. The ether was removed by distillation during 2 hr. and the mixture then boiled under reflux for another hour. It then had a neutral reaction to litmus. Water was added and the oil extracted with ether, dried, and twice distilled under reduced pressure. The main fraction (15·3 g., 60%) had b. p. 166—170°/1 mm. In addition a small fraction (2·6 g.) with b. p. <100°/1 mm. was obtained and also a fraction (4·2 g.) distilling over a considerable range from which, after hydrolysis, a little more acid was subsequently isolated. Distillation was stopped when the residue in the distilling flask began to decompose. The bromide ion in the aqueous solution was estimated gravimetrically and found to be 96·2% of the total bromine originally present.

The ester was hydrolysed with boiling ethanolic potassium hydroxide, and the resultant acid crystallised from aqueous ethanol. It had m. p. *ca.* 218° (decomp.), not depressed on admixture with **3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1 : 1-dicarboxylic acid** (Found: C, 72·6; H, 5·2. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0%). The yield of crystallised material was 9·65 g. (46% from the dibromide).

The acid was decarboxylated by heating it at 230°. The product crystallised from ethanol in rods, m. p. 161—162° (Found: C, 80·6; H, 6·1%; *M*, 490; equiv., 247. Calc. for $C_{16}H_{14}O_2$: C, 80·65; H, 5·9%; *M*, 238; equiv., 238). The acid is thus dimeric in benzene. A mixed m. p. with **3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylic acid** was 161—162°. The methyl ester had m. p. 46—47° [Found: C, 80·9; H, 6·5%; *M* (in *cyclo*hexane), 244. Calc. for $C_{17}H_{16}O_2$: C, 80·9; H, 6·4%; *M*, 252]. Light absorption for the acid in 96% ethanol: $\lambda_{max.}$ 249 mμ (ε 15,300), $\lambda_{min.}$ 228 mμ (ε 5550); cf. data in Table.

In another preparation on the same scale the crude ester was hydrolysed without initial

distillation. The crude acid so obtained was difficult to purify. Oily (acidic) impurities were removed by treatment with a little boiling benzene (in which the required acid is practically insoluble) and 10·8 g. (51%) of good-quality dicarboxylic acid were eventually obtained.

In another preparation only half the calculated quantity of ethyl propane-1 : 1 : 3 : 3-tetracarboxylate was used. The crude ester was hydrolysed and eventually a 30% yield (based on dibromide used) of nearly pure dicarboxylic acid was obtained. But 92·5% of the total bromine was present as bromide ions at the end of the reaction.

2 : 2′-*Di*-(2 : 2-*diethoxycarbonyl*-n-*propyl*)*diphenyl* (VIII).—Sodium (2·8 g., 2 atom-equivs.) was dissolved in ethanol (150 c.c.) and ethyl methylmalonate (Cox and McElvain, *Org. Synth.*, Coll. Vol. II, pp. 272, 279) (20·5 g., 2 mols.) added, immediately followed by powdered 2 : 2′-bisbromomethyldiphenyl (20 g., 1 mol.). Immediate separation of sodium bromide occurred. The mixture was heated under reflux for 3 hr. Some ethanol was distilled off; the residue was poured into water and the solid ester filtered off. 2 : 2′-*Di*-(2 : 2-*diethoxycarbonyl*-n-*propyl*)-*diphenyl* crystallised from ethanol in needles, m. p. 107° (25 g., 81%) (Found : C, 68·5; H, 7·3. $C_{30}H_{38}O_8$ requires C, 68·4; H, 7·3%).

2 : 2′-*Di*-(2-*carboxy*-n-*propyl*)*diphenyl*.—The above ester was hydrolysed by boiling with ethanolic potassium hydroxide, and the resultant tetracarboxylic acid, m. p. 200° (decomp.), heated at 220° for 30 min. The residue was dissolved in 10% aqueous sodium carbonate, and the extract, after being washed with ether, was acidified. The precipitate was washed with light petroleum (b. p. 60—80°). 2 : 2′-*Di*-(2-*carboxy*-n-*propyl*)*diphenyl* crystallised from benzene in prisms, m. p. 155—158° with some previous softening, and was presumably a mixture of diastereoisomers (Found : C, 73·8; H, 6·7. $C_{26}H_{22}O_4$ requires C, 73·6; H, 6·8%) (yield, 11·6 g., 60% from the dibromide). The *diethyl ester* had b. p. 194—196°/3 mm., n_D^{25} 1·5248 (Found : C, 75·3; H, 7·6. $C_{34}H_{38}O_4$ requires C, 75·3; H, 7·9%). The *dimethyl* ester crystallised from aqueous ethanol in rectangular plates, m. p. 68° (Found : C, 74·5; H, 7·7. $C_{32}H_{34}O_4$ requires C, 74·5; H, 7·4%).

Absorption Spectra.—Spectra were measured on an automatic recording spectrophotometer (cf. Part I, *loc. cit.*) and on Unicam SP. 500 manual instruments. Fine-structure features were

Ultraviolet absorption spectra.

Compound	Short-wave band				Conjugation band		Long-wave features	
	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{infl.}$	$\varepsilon_{infl.}$
3 : 4-5 : 6-Dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylic acid (I; R = H)	205	43,000	228	5770	249	15,300	(*ca.* 274)	*ca.* 1750
Methyl 3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene-1-carboxylate (I; R = Me)	207·5	42,500	227·5	5700	248·5	15,500	(*ca.* 274)	*ca.* 1700
1-Hydroxymethyl-3 : 4-5 : 6-dibenzo-*cyclo*hepta-3 : 5-diene (II)	205·5	43,000	227·5	5400	248·5	15,400	(*ca.* 269) (*ca.* 277)	*ca.* 3200 *ca.* 1500
Ethyl 4 : 5-6 : 7-dibenzo*cyclo*octa-4 : 6-diene-1 : 2 : 2-tetracarboxylate (III)	215	43,400	230·5	10,900	239·5	13,100	(269) (278)	765 475
Methyl 4 : 5-6 : 7-dibenzo*cyclo*octa-4 : 6-diene-1 : 2-dicarboxylate (IV; R = Me), m. p. 139—141°	212·5	43,300	227·5	10,250	236·5	12,700	(266) (274)	810 492
Methyl 4 : 5-6 : 7-dibenzo*cyclo*octa-4 : 6-diene-1 : 2-dicarboxylate (IV; R = Me), m. p. 126·5—128°	213	45,600	229	10,950	236·5	12,150	(267) (275)	760 480
2 : 2′-Di-(2-methoxycarbonyl-n-propyl)diphenyl	(*ca.* 206?)	36,000	—	—	(230)	6050	(261) (270·5)	615 405

Solvent, 96% ethanol; wavelengths ($m\mu$) in parentheses denote inflections.

confirmed by the moving-plate logarithmic cam method (Holiday, *J. Sci. Inst.*, 1937, **14**, 166) but the wavelengths given in the Table for inflections are the values obtained by direct examination of large-scale plots.

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The Solubilities and Heats of Crystallisation of Sucrose and Methyl α-D-Glucoside in Aqueous Solution.

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The solubilities and heats of crystallisation of sucrose and methyl α-D-glucoside have been determined over the temperature range 20—80° by a new method. The heats of crystallisation have been calculated from these results and activity data.

In a new method of determining the solubility of solids described by Dauncey and Still (*J. Appl. Chem.*, 1952, **2**, 399) the saturation temperature of a solution of fixed concentration is determined within only a few minutes. This is useful in determining the solubility of sucrose in water where decomposition becomes important at the higher temperatures if the experiments are too prolonged, and where equilibrium is reached only after many hours at lower temperatures. Previous determinations of the solubility of sucrose have given results which are not in complete agreement (*e.g.*, *Nat. Bur. Stand.*, Circular C440, 1942, p. 359).

Heats of crystallisation are readily calculated from solubility and activity data (Williamson, *Trans. Faraday Soc.*, 1944, **40**, 435). The heat of crystallisation of sucrose has therefore been calculated and, for comparison, that of methyl α-D-glucoside for which activity data exist. No solubility data appear to be available however, so that the solubility of methyl α-D-glucoside has been determined in the same way as that of sucrose.

Experimental

The sucrose used was selected granulated sugar of reducing sugar content less than 0·02% and ash content less than 0·01%. About 1 l. of a 50% solution of sucrose was concentrated at 60° at a water-pump, until a convenient concentration was reached as determined by a refractometer. The temperature of the solution was then quickly raised and the flask removed and fitted with a wash-bottle head. The contents were well shaken and then transferred through the tube of the head to the solubility cell.

This consisted of a 2″ T-piece pipe-fitting which had been machined smooth and silver-plated. Its capacity was about 100 ml. The end faces carried Perspex discs with a rubber gasket between them. The short upright arm of the T-piece carried a rubber stopper through which passed a stainless-steel stirrer, a thermometer graduated in 0·1°, and the entry tube for the solution. The last was joined to the tube of the wash-bottle head through a ground-glass joint which was normally closed with a stopper. The whole cell was contained in a Perspex box, about 4″ × 4″ × 6″, through which water was circulated by a centrifugal pump. Included in the system of circulating water was a conical flask which could be heated or cooled, thus adjusting the temperature of the sucross solution in the cell. There was very little lag between the temperature of the well-stirred sucrose solution and that of the circulating water.

On the outside of the Perspex box was a slit formed by two razor blades behind which was placed a 40-w. lamp. When the cell was assembled a sucrose crystal was clipped to the thermometer with a rubber band. By viewing the slit behind the crystal the saturation temperature of the sucrose solution could be determined as described by Dauncey and Still (*loc. cit.*). The solution was heated or cooled through the saturation temperature a number of times and the average value determined for each solution. Readings agreed to within 0·1—0·2°. The stem correction for the thermometer amounted to 0·5° at 90°.

After the saturation temperature had been determined, a sample of the solution was removed by a pipette from the solubility cell and transferred to a weighed 50-ml. flask through a glass sleeve to prevent sucrose solution from adhering to the neck of the flask. The flask was then quickly closed with a rubber stopper and allowed to cool. The weight of sucrose solution was determined by weighing and the contents of the flask were made up to volume. This was carried out in an air-conditioned room. The sucross concentration was then read in a Hilger polarimeter.

A sample of this diluted solution was taken for determination of reducing sugar by a modified ferricyanide method (J. H. Williams, unpublished work) which is insensitive to the presence of large amounts of sucrose.

In a separate series of experiments, no effect could be found due to rate of heating or cooling of the sucrose solution. The rates used in the experiments were less than 1·5° per min.

The experiments with methyl α-D-glucoside were carried out in the same way as those with sucrose. The material used had m. p. 165° and $[\alpha]_D^{20}$ +158·8° (cf. Rüber, *Ber.*, **1924**, **57**, 1797: m. p. 166°, $[\alpha]_D^{20}$ +158·9°).

Results

The results obtained with sucrose are shown in Table 1. These have been fitted by the method of least squares to a power series equation giving $C = 62{\cdot}77 + 0{\cdot}1706t + 0{\cdot}000344t^2$, where C is the saturation concentration (g. of sucrose per 100 g. of solution), and t is the saturation temperature.

Table 1. *Solubility of sucrose in water.*

Concn. (g./100 g. soln.)	Satn. temp.	Sucrose inverted (%)	Concn. (g./100 g. soln.)	Satn. temp.	Sucrose inverted (%)	Concn. (g./100 g. soln.)	Satn. temp.	Sucrose inverted (%)
66·09	18·5°	—	72·51	51·1°	0·020	75·80	66·4°	—
66·97	23·9	—	72·72	52·2	—	75·95	66·5	0·021
66·89	24·4	—	72·76	52·6	—	76·07	68·2	—
67·23	24·9	—	73·04	53·6	0·016	76·03	69·0	0·015
67·21	25·9	—	73·05	53·8	—	76·32	70·1	0·021
68·36	30·0	—	72·78	54·1	—	76·45	70·4	—
68·31	30·5	0·026	73·16	55·8	—	77·06	72·8	—
68·73	31·5	—	73·50	56·1	—	76·98	73·8	0·025
68·62	33·1	—	73·72	56·4	—	77·60	74·5	—
69·32	34·5	—	73·64	57·5	—	77·52	74·6	—
69·42	36·0	—	73·74	57·8	—	77·58	75·1	—
69·41	36·4	—	73·68	58·4	—	78·40	79·5	—
70·17	40·2	—	74·10	58·6	—	78·86	82·3	—
70·23	40·7	—	74·15	59·7	0·015	79·85	85·1	0·016
70·35	41·0	0·024	74·48	61·1	—	79·94	85·3	—
70·55	42·2	—	74·47	61·4	—	79·99	85·5	0·023
70·74	42·3	—	74·69	62·6	—	80·22	86·6	—
71·63	46·1	—	74·93	62·9	0·018	80·32	88·0	—
72·12	49·6	—	75·05	64·6	—	80·87	90·2	0·014
71·91	50·2	0·017	75·43	65·5	—			

The results for methyl α-D-glucoside are shown in Table 2. These were fitted to the equation $C = 44{\cdot}86 + 0{\cdot}2495t + 0{\cdot}00120t^2$.

Table 2. *Solubility of methyl α-D-glucoside.*

Concn.	70·90	68·78	66·70	66·08	65·25	64·71	64·02	62·40	61·48	60·79	59·78
Temp.	78·0°	73·2	67·8	66·2	64·2	62·7	60·6	57·3	54·4	51·8	49·6
Concn.	59·42	57·31	55·33	54·48	53·42	52·41	52·36	51·59	51·20	49·38	
Temp.	49·0°	43·2	37·2	33·9	31·8	27·3	26·6	25·5	22·5	17·8	

Discussion

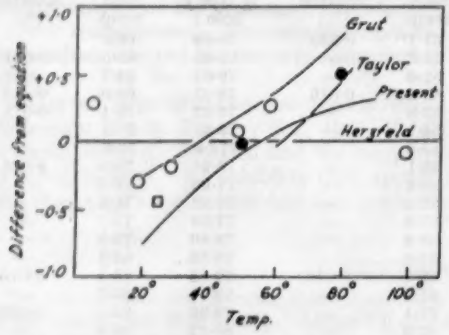
Solubility Results.—The present results for sucrose are compared with those of other workers in the Figure, where the difference between the saturation concentrations and those given by the equation $C = 64{\cdot}18 + 0{\cdot}1348t + 0{\cdot}000531t^2$ is plotted as a function of temperature. This equation is the smoothed curve through Herzfeld's results (*Z. ver. Rübenz.-Ind.*, 1892, **42**, 181). It will be seen that the present results deviate fairly considerably from this equation, especially at the lower temperatures. Herzfeld's experimental results, also plotted, do not fit the smoothed equation very well. The four results at intermediate temperatures fall on a curve lying parallel to and slightly above the present results. At 5·2° the determined saturation concentration, which was approached from supersaturated solution, is apparently too high.

Grut (*Z. Zuckerind. cechoslovak. Rep.*, 1937, **61**, 356) determined the solubility of sucrose at 10° intervals from 20° to 80°. The general trend of his results is in agreement with the

present results and Herzfeld's experimental results at intermediate temperatures, although the saturation concentrations are all higher than those we have found.

There are isolated determinations at 25° by Scatchard, Hamer, and Wood (*J. Amer. Chem. Soc.*, 1938, **60**, 3061) and at 50° and 80° by Hruby and Kasjanov (*Intern. Sugar J.*, 1940, **42**, 21), the latter being the average of ten determinations. These agree fairly well with the present results.

Probably the best solubility results for sucrose are those of Taylor (*J.*, 1947, 1678). They cover a rather narrow temperature range, but within this are in good agreement with ours. There is a slight deviation above 75°, probably due to the fact that for the two experiments which Taylor carried out above 80° inversion was more serious than at the lower temperatures. Inversion is not significant for the present results, however, as the concentrated sucrose solutions were prepared by vacuum-distillation at moderate temperatures and not by dissolving solid sucrose at temperatures about 10° above the saturation temperatures, the method used by Taylor. Moreover, the determination of the saturation temperature required only a short time by the present method.



Comparison of various determinations of sucrose solubility.

The full lines represent smoothed values. Experimental results are expressed as follows:

○ Herzfeld; ● Hruby and Kasjanov; □ Scatchard, Hamer, and Wood.

Heats of Crystallisation of Sucrose and Methyl α-D-*Glucoside.*—Williamson (*loc. cit.*) has given a convenient summary of the formulæ for combining solubility and activity data to give heats of crystallisation. For activity data the following have been used. For sucrose at 25° the isopiestic data quoted by Harned and Owen ("Physical Chemistry of Electrolytic Solutions," Reinhold, New York, 1950, p. 289), for methyl α D-glucoside at 30° the vapour pressure data given by Berkeley *et al.* (*Phil. Trans.*, 1919, **218**, *A*, 295), and at 60° and 90° unpublished vapour-pressure data of R. W. Jackson (sucrose) and W. J. Read (methyl α-D-glucoside) provided by Dr. W. J. Dunning.

The calculated heats of crystallisation are shown below in Table 3. The heats of crystallisation of the two sugars are approximately equal and increase markedly with temperature. (cf. Davies and Griffiths, *Trans. Faraday Soc.*, 1953, **49**, 1405).

TABLE. 3. *Calculated heats of crystallisation.*

Temp.	25°	30°	60°	90°
Sucrose (kJ/mole)	12·2	—	18·8	31·8
Methyl α-D-glucoside (kJ/mole)	—	15·5	18·5	31·0

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Studies in Pyrolysis. Part IV. Model Systems for the Pyrolysis of Poly(ethylene Terephthalate) and Allied Polyesters.*

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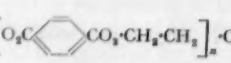
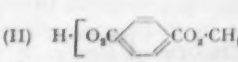
Ethylene dibenzoate breaks down in the vapour phase (*ca.* 400—550°) by two competitive routes: (i) a major alkyl–oxygen scission (A^1) to benzoic acid and vinyl benzoate, and (ii) a minor disproportionation (D) to benzoic anhydride and acetaldehyde. The vinyl benzoate formed then pyrolyses by three competitive routes: (i) a major thermal rearrangement (R) to benzoylacetaldehyde, which then undergoes decarbonylation (C^1) to carbon monoxide and acetophenone; (ii) a minor alkenyl–oxygen scission (A^2) to benzoic acid and acetylene; and (iii) a minor decarboxylation (C^2) to carbon dioxide and styrene. Separate pyrolysis of benzoylacetaldehyde confirms the R/C^1 stage. Acyl–oxygen scission of vinyl benzoate to benzaldehyde and keten does not occur; but aliphatic vinyl esters (*e.g.*, acetate and *iso*butyrate) are pyrolysed not only *via* routes A^2, C^2, and R/C^1, but also by a fourth competitive route—a major acyl–oxygen scission (B^1) to acetaldehyde and a keten corresponding to the acyl group. The bearing of these results on the pyrolysis of cognate polyesters is discussed.

The thermal stability of various synthetic polyesters, such as poly(ethylene maleate) and the polyester fibres (*e.g.*, "Terylene" and "Dacron") based on poly(ethylene terephthalate) (I), is of great technological importance. Various studies on the thermal degradation of the latter polymer have been published, but the precise mechanism of breakdown remains obscure. Pohl (*J. Amer. Chem. Soc.*, 1951, **73**, 5660) followed the change by measuring the rate of gas-evolution, and showed that at *ca.* 300° in the absence of oxygen the polyester undergoes random main-chain scission, with progressive reduction in molecular weight. The pyrolysate contained acetaldehyde, water, and carbon dioxide, as well as carboxyl and anhydride groups. He deduced that a principal point of weakness in the chain is the β-methylene group, since the polyester (I) is markedly less thermostable than its analogue (II), which possesses no β-hydrogen atoms.

(I)  (II) 

Marshall and Todd (*Trans. Faraday Soc.*, 1953, **49**, 67) studied the kinetics of the degradation (*ca.* 280—320°) by following changes in the viscosity of the molten material. Like Pohl, they deduced a random chain scission, probably at the ester linkages, giving rise to one carboxyl group per scission, and detected acetaldehyde and carbon dioxide in the pyrolysate. In addition, they detected carbon monoxide, terephthalic acid, and another solid product (not positively identified). They concluded that degradation is essentially free-radical in character, and outlined a tentative sequence of propagation reactions.

These quantitative studies cannot yet be fully interpreted, however, in the absence of a full *qualitative* identification of the degradation products. The present work was planned to provide this identification.

Difficulties encountered in preliminary experiments with the polyester (I) itself suggested as a promising alternative approach the pyrolysis of simplified model systems representing (i) specific segments (*e.g.*, III, IV, V) from within the intact polyester chain (I); (ii) terminal segments of (I) bearing hydroxyl (*e.g.*, VI) and carboxyl end-groups; and (iii) terminal segments of the pyrolysed chain bearing new end-groups which might be predicted *a priori* (*e.g.*, VII). The reasons for selecting (III), (IV), and (VI) are evident from formula (I), while (V) represents the known incorporation of occasional ether linkages (*e.g.*, diethylene glycol

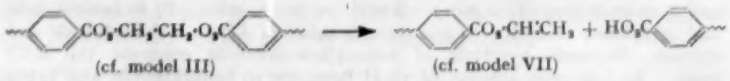
* Part III, *J.*, 1935, 1054.

units) into the original chain during polycondensation. Vinyl benzoate (VII) was selected because the model compound (III) had been reported to yield vinyl benzoate and benzoic acid when pyrolysed at 360—425° (Chitwood, U.S.P. 2,251,983/1941), in conformity with

(III) $BzO{\cdot}CH_2{\cdot}CH_2{\cdot}OBz$ (IV) $BzO{\cdot}CH_2{\cdot}CH_2{\cdot}O_2C{-}C_6H_4{-}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}OBz$

(V) $BzO{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}OBz$ (VI) $BzO{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ (VII) $BzO{\cdot}CH{:}CH_2$

the normal pyrolytic scission to olefin and carboxylic acid undergone by simple alkyl carboxylates (cf. Hurd, " The Pyrolysis of Carbon Compounds," Chemical Catalog Co., New York, 1929, Chap. 17). This clearly suggests that each random chain-scission should generate concurrently a carboxyl end-group (cf. Marshall and Todd, *loc. cit.*) and a vinyl ester end-group, for which vinyl benzoate is an obvious model, thus :



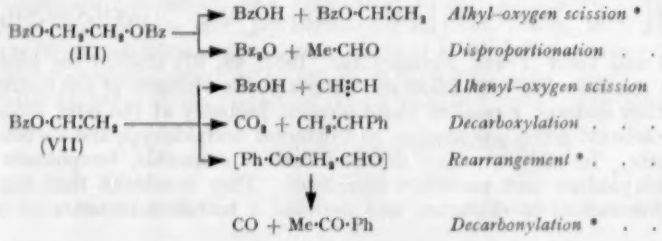
(cf. model III) (cf. model VII)

Re-investigation of Chitwood's results by Allan and Ritchie (*Chem. and Ind.*, 1953, 747) showed that the vinyl benzoate and benzoic acid produced from ethylene dibenzoate on pyrolysis are accompanied by carbon monoxide and acetophenone, and that these by-products, not recorded by Chitwood, are also formed on pyrolysis of vinyl benzoate alone. The results strongly suggested that vinyl benzoate is pyrolysed by primary thermal rearrangement into its isomeric β-keto-aldehyde, benzoylacetaldehyde (VIII), and that this, in turn, yields acetophenone by the normal pyrolytic decarbonylation of aldehydes (cf. Hurd, *op. cit.*, Chap. 10) :

$BzO{\cdot}CH{:}CH_2 \longrightarrow [Ph{\cdot}CO{\cdot}CH_2{\cdot}CHO]$ (VIII) . . . . . *Rearrangement*

$\longrightarrow CO + Me{\cdot}CO{\cdot}Ph$ . . . . . *Decarbonylation*

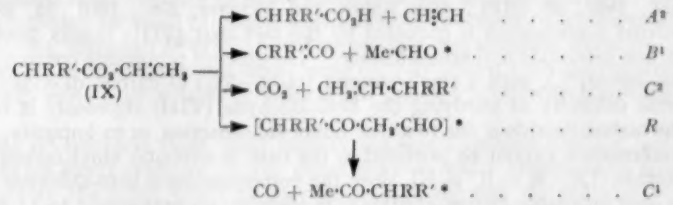
Extension of these studies has now shown that the pyrolysis of ethylene dibenzoate and vinyl benzoate at *ca.* 400—550°, in a Pyrex-glass flow-reaction vessel, is even more complicated than at first thought. The constituents now identified in the complex pyrolysates from (III) and (VII), and their relative abundance, are best accounted for by the following series of competitive and consecutive reactions, where * indicates the predominant routes :


BzO·CH₂·CH₂·OBz
(III)
BzOH + BzO·CH:CH₂ Alkyl–oxygen scission * . . . A¹
Bz₂O + Me·CHO Disproportionation . . . . D
BzO·CH:CH₂
(VII)
BzOH + CH:CH Alkenyl–oxygen scission . . A²
CO₂ + CH₂:CHPh Decarboxylation . . . . . C²
[Ph·CO·CH₂·CHO] Rearrangement * . . . . . R
CO + Me·CO·Ph Decarbonylation * . . . . C¹

With the exception of benzoylacetaldehyde, all the products shown above were identified in the pyrolysate from (III); in addition, benzene, methane, and small amounts of ethylene were detected. Benzene and methane are readily accounted for as secondary breakdown products of benzoic acid (from A^1 and A^2) and acetaldehyde (from D) respectively; but no obvious route suggests itself for the formation of ethylene, and this product [from (III) and (VII), but not (VIII)] still remains unexplained.

Just as vinyl benzoate is a suitable model compound for studying the pyrolysis of the aromatic polyester (I), so also can aliphatic vinyl carboxylates such as vinyl acetate (IX; R = R′ = H) and *iso*butyrate (IX; R = R′ = Me) be used to study the end-groups which are formally possible if a purely aliphatic polyester [*e.g.*, poly(ethylene maleate)] also undergoes primary alkyl–oxygen scission. It has now been found that at *ca.* 500—550°

the ester (IX) breaks down by the following system of four concurrent competing primary scissions, where • again indicates the predominant routes :

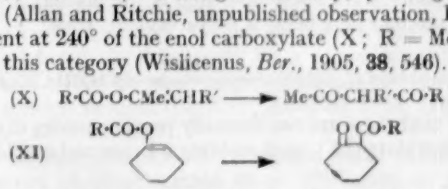


Three of these primary routes (A^2, C^2, and R/C^1) are parallel to those found for vinyl benzoate : but a major acyl–oxygen scission (B^1) now appears, which has no counterpart with the aromatic ester. With the exception of the β-keto-aldehyde, all the products shown were identified in the pyrolysate from (IX) ; in addition, there were small quantities of methane and ethylene, which are subject to the comments made above on the pyrolysate from the ester (III).

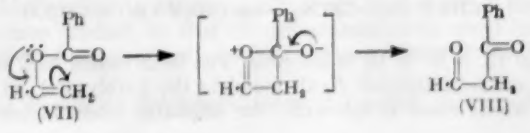
No systematic search was made for specific catalytic effects at the wall of the reaction vessel ; but comparative runs were made with vinyl acetate in three vessels constructed respectively of Pyrex glass, Vitreosil, and stainless steel. For the first two, the results were qualitatively the same, though Vitreosil somewhat enhanced route R/C^1 at the expense of B^1 (see Table 4) ; but the gaseous pyrolysate from the stainless-steel vessel contained some 46% of hydrogen. A similar experiment with vinyl benzoate in a stainless-steel vessel also yielded hydrogen (*ca.* 12%). Several sources of this hydrogen are possible ; but it probably arises from (VII) mainly by a catalysed pyrolysis of the ethylene which has been shown to occur in the pyrolysate from vinyl carboxylates. Pure ethylene, pyrolysed under the same conditions in the same vessel, yielded hydrogen and paraffin (calculated as methane) in almost the same molar ratio (1 : 1·9) as that observed in the gaseous pyrolysate from vinyl benzoate itself (1 : 1·8). In the pyrolysis of vinyl acetate, a further important source of hydrogen is probably the acetone formed *via* route R/C^1 : for acetone, pyrolysed alone under the same conditions, yielded a large amount of hydrogen.

Discussion

Route R/C¹.—The mechanism of the unexpected conversion of vinyl carboxylates into carbon monoxide and a methyl ketone, which is the most important result emerging from the present work, is suggested by the fact that many enol carboxylates (*e.g.*, X ; R = Me or Ph, R' = H : XI ; R = Me) undergo intramolecular rearrangement at *ca.* 500° to an isomeric β-diketone (Boese and Young, U.S.P. 2,395,800/1946 ; B.P. 615,523/1949 ; Young, Frostick, Sanderson, and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**, 3635). *cyclo*Hex-1-enyl benzoate (XI ; R = Ph) rearranges similarly, yielding chiefly 2-benzoyl*cyclo*hexanone at *ca.* 480° (Allan and Ritchie, unpublished observation, 1953) ; and an analogous thermal rearrangement at 240° of the enol carboxylate (X ; R = Me, R' = CO_2Et) provides a further example in this category (Wislicenus, *Ber.*, 1905, **38**, 546).



Young *et al.* (*loc. cit.*) proposed a plausible intramolecular mechanism for the thermal rearrangement of enol carboxylates, *via* a cyclic transition state, which can be applied to vinyl benzoate as follows :



No *direct* evidence for this rearrangement was obtained by Allan and Ritchie (*loc. cit.*), which is not surprising in view of the known instability of (VIII) (Claisen and Fischer, *Ber.*, 1887, **20**, 2191; von Bülow and Sicherer, *Ber.*, 1901, **34**, 3889). Nevertheless, *indirect* confirmation is provided by the fact that (VIII) breaks down at 400—550° into carbon monoxide and acetophenone. The gaseous pyrolysate consists of carbon monoxide (*ca.* 95—97%), with a small amount (*ca.* 2—5%) of carbon dioxide; but in view of the great difficulty of purifying the keto-aldehyde (VIII) rigorously it is uncertain whether the carbon dioxide is due to a true minor side-reaction, or to impurity. Even this indirect confirmation cannot be provided in the case of aliphatic vinyl carboxylates such as vinyl acetate (IX; R = R′ = H), since the corresponding β-keto-aldehyde (acetoacetaldehyde) is here incapable of free existence, condensing spontaneously to 1 : 3 : 5-triacetylbenzene (Claisen and Stylos, *Ber.*, 1888, **21**, 1144). Nevertheless, the most convincing explanation of the observed acetone (from vinyl acetate) and methyl *iso*propyl ketone (from the *iso*butyrate) is once again route R/C^1.

The previously unexplained by-products reported by Chitwood (*loc. cit.*) in the pyrolysis of ethylene diacetate and dipropionate can now be readily accounted for on the basis of competing A^2, B^1, C^2, and R/C^1 scissions of vinyl carboxylates. For example, the formation of ethyl methyl ketone from ethylene dipropionate can be attributed to secondary R/C^1 breakdown of vinyl propionate, thus:

$$\text{Et·CO}_2\text{·CH:CH}_2 \xrightarrow{R} [\text{Et·CO·CH}_2\text{·CHO}] \xrightarrow{C^1} \text{CO} + \text{Me·CO·Et}$$

When the acetophenone content of the pyrolysate from vinyl benzoate is plotted against reaction temperature (range 300—550°) the relationship is almost linear (see Table 2); and extrapolation to zero acetophenone content suggests *ca.* 190° as the threshold temperature for decomposition—*i.e.*, slightly below the b. p. of vinyl benzoate (203°/760 mm.). Since the usual preparations of this ester entail either a vapour-phase reaction, or some other high-temperature process, and since vinyl benzoate and acetophenone have almost the same b. p., the preparation of really pure ester is likely to be difficult. It has, in fact, now been found that vinyl benzoate prepared at *ca.* 300—350° by the catalysed vapour-phase addition of acetylene to benzoic acid (B.P. 581,501/1946) contains up to *ca.* 7% of acetophenone.

Routes A^1 *and* A^2.—Alkenyl–oxygen scission (A^2) of an alkenyl carboxylate to an acetylene and a carboxylic acid does not seem to have been observed previously, although alkyl–oxygen scission (A^1) is a well-established major route (though not the only one) in the pyrolysis of alkyl carboxylates. It is of interest that, although monomeric vinyl acetate breaks down thermally by four competitive routes (A^2, B^1, C^2, and R/C^1), yet its polymer has been shown by Grassie (*Trans. Faraday Soc.*, 1952, **48**, 379; 1953, **49**, 835) to break down *in vacuo* at *ca.* 215—235° almost wholly by evolution of acetic acid, *via* a non-radical chain reaction. Each successive step is the normal A^1 scission of an alkyl carboxylate, the olefinic product here being a polyacetylene, thus:

$$\sim\!\text{CH}_2\text{·CH(OAc)·CH}_2\text{·CH(OAc)}\sim \xrightarrow{-\text{AcOH}} \sim\!\text{CH:CH·CH:CH}\sim$$

Route B^1.—It is clear that there are two formally possible modes of acyl–oxygen scission of an aliphatic vinyl carboxylate (IX), each yielding a keten and an aldehyde, thus:

$$\text{CHRR′·CO·O·CH:CH}_2 \longrightarrow \text{CRR′:CO} + (\text{HO·CH:CH}_2 \rightleftharpoons \text{Me·CHO}) \quad . \quad . \quad . \quad B^1$$

$$\text{CHRR′·CO·O·CH:CH}_2 \longrightarrow \text{CHRR′·CHO} + \text{CH}_2\text{:CO} \quad . \quad . \quad . \quad . \quad . \quad B^2$$

For vinyl acetate (R = R′ = H) it happens that both routes lead to the same pair of products, keten and acetaldehyde (both found in the pyrolysate), so that here it is not possible to say which route is followed; for aliphatic esters higher than the acetate,

however, routes B^1 and B^2 are no longer equivalent. It is found that vinyl *iso*butyrate (R = R′ = Me) yields acetaldehyde and secondary products attributable to dimethylketen (route B^1), with no detectable quantity of *iso*butyraldehyde and keten (route B^2). Route B^1 is structurally precluded for vinyl benzoate, which lacks the necessary α-hydrogen atom in the acyl group; yet, although B^2 is still formally possible, the benzoate shows no type of acyl–oxygen scission, benzaldehyde and keten being entirely absent from the pyrolysate. The inference is that vinyl carboxylates in general can undergo acyl–oxygen scission by route B^1 only.

Only one of the B^1 products from vinyl *iso*butyrate was identified directly (acetaldehyde); there was no direct evidence for the dimethylketen which should have accompanied it. Presumably the latter failed to survive passage through the reaction vessel at 550°; and it has, in fact, been shown to break down at high temperatures into propene and 2 : 3-dimethylbut-2-ene (Staudinger, "Die Ketene," F. Enke, Stuttgart, 1912, p. 142; Staudinger and Endle, *Ber.*, 1913, **46**, 1437).

The gaseous pyrolysate from vinyl *iso*butyrate contained both propene and 2 : 3-dimethylbut-2-ene, which very strongly confirms that dimethylketen is a transient primary product in the pyrolysis.

In addition to the various constituents detailed previously, the pyrolysate from vinyl acetate contained a small amount of acetic anhydride, whereas that from vinyl *iso*butyrate contained no acid anhydride. The acetic anhydride may have arisen either by combination of acid (from A^2) with keten (from B^1), or by direct pyrolysis of the acid (cf. Davidson and Newman, *J. Amer. Chem. Soc.*, 1952, **74**, 1515). The former explanation is favoured by the absence of *iso*butyric anhydride; for although keten itself largely survives passage through the reaction vessel, the much less stable dimethylketen is represented only by its breakdown products, and would therefore not be expected to combine significantly with the free *iso*butyric acid.

Route C^2.—From vinyl *iso*butyrate, route C^2 should have yielded carbon dioxide and 3-methylbut-1-ene. The latter could not be identified positively from the infrared spectrum of the gaseous pyrolysate, owing to masking effects; but two of its isomers were identified, *viz.*, 2-methylbut-1-ene (weak) and 2-methylbut-2-ene (strong), and it is highly probable that these are due to thermal isomerisation of the primary olefin to a mixture of isomeric pentenes.

The direct decarboxylations of esters recorded in this paper are of considerable interest; for, although thermal decarboxylation of acids is well established, only very few esters have been reported to show this behaviour (see, *e.g.*, Skraup and Beng, *Ber.*, 1927, **60**, 942).

Route D.—The formation of small amounts of benzoic anhydride and acetaldehyde from the ester (III) cannot be attributed to secondary breakdown of substances (VII) and (VIII) as intermediates, since neither yields the anhydride or aldehyde when pyrolysed separately under the same conditions. Further, although Davidson and Newman (*loc. cit.*) have demonstrated the pyrolytic production of anhydrides from a wide range of carboxylic acids, including benzoic acid, conversion of this acid into its anhydride is insignificant under the conditions now employed. It therefore seems that benzoic anhydride and acetaldehyde must be produced simultaneously by a minor competitive scission (*D*) of (III), analogous to certain other thermal disproportionations whereby esters yield an acid anhydride as one scission product (Geuther, *Annalen*, 1858, **106**, 249; Hurd and Bennett, *J. Amer. Chem. Soc.*, 1929, **51**, 1197).

It may be noted that Deutsch and Hermann (G.P. 515,307/1927), who briefly described the breakdown of vinyl acetate at *ca.* 470° over an activated carbon catalyst, recorded that, in addition to constituents which have all now been observed in the uncatalysed thermal decomposition of the ester (acetaldehyde, acetone, keten, acetic acid and anhydride, and unspecified hydrocarbons), the pyrolysate also contained "vinyläther." It should therefore be emphasised that no divinyl ether was observed in any of the pyrolyses now studied, so that disproportionation of vinyl carboxylates to acid anhydride and divinyl ether is not one of the purely thermal competitive breakdown routes.

Application of Results to Polyesters.—Since the model compounds studied were all

pyrolysed in the vapour phase, the results must be applied with some caution in interpreting the recorded pyrolyses of poly(ethylene terephthalate), which were effected with molten polymer. Nevertheless, our results suggest a straightforward explanation for many previous observations—for example, (i) the copious evolution of carbon monoxide on pyrolysis of poly(ethylene terephthalate) (a fact not hitherto explained, and not mentioned by Pohl, *loc. cit.*), (ii) the formation of carboxyl and anhydride groups and of acetaldehyde, and (iii) the absence of vinyl ester groupings from the pyrolysate (Pohl, *loc. cit.*; Marshall and Todd, *loc. cit.*; Gilchrist and Ritchie, unpublished observations, 1951). One consequence of this last observation requires emphasis. Chitwood (*loc. cit.*) pyrolysed the ester (III) by refluxing it at 360—425°, using a take-off head at 220—245° to remove vinyl benzoate as formed. In other words, the contact time was comparatively short; and it was shorter still in the vapour-phase flow-reaction vessels now used. Under these conditions, most of the vinyl benzoate formed in the primary scission remained undecomposed; whereas in experiments with molten poly(ethylene terephthalate) (cf. Marshall and Todd, *loc. cit.*), the effective "contact time" is very great, facilitating destruction of any primary vinyl ester groups by secondary pyrolysis of the type now described. On this basis, ketonic products would be expected to accumulate in the molten polyester; and this prediction is now under investigation.

The pyrolysis of the model compounds (IV), (V), and (VI) will be described in later communications.

Experimental

Apparatus.—Five different reaction vessels were used—three of Pyrex glass (P.1, P.2, P.3), one of stainless steel (S), and one of Vitreosil (V). The first four were packed with Pyrex-glass helices, and the fifth with coarsely crushed Vitreosil; P.1, S, and V had approximately the same dimensions (length 65 cm., bore 2 cm.); P.3 had the same bore, but was only 30 cm. long; P.2 was 65 cm. long, with a central section (length 18 cm.) of 2-cm. bore, and inlet and outlet sections of 1-cm. bore.

Each vessel was supported vertically inside a cylindrical electric furnace, which kept the central section of the reaction vessel (about half of its length) at a temperature controlled (±5°) by a Variac transformer, and measured by a chromel–alumel thermocouple in a pocket located axially within the reaction vessel. Before each pyrolysis the system was several times evacuated and filled with nitrogen, to avoid combustion of the vapours. The pyrolysand was run into the vessel from a tap-funnel fitted with the usual device for equalising pressures above and below the feed-liquid, and enclosed in a heating jacket to melt solid materials (*e.g.*, III). Liquid (and solid) pyrolysates were collected in a first receiver, *via* an inclined air-condenser; the exit-gases were then passed through a water-condenser to a second receiver cooled in Drikold–acetone; the final uncondensed gases were then passed (through specific reagent-traps as required) to an automatic device which collected them over saturated aqueous magnesium chloride.

Analytical Methods: Results.—Aldehydes and ketones were estimated by Iddles and Jackson's method (*Ind. Eng. Chem. Anal.*, 1934, **6**, 454), and, unless otherwise stated, were identified by their 2:4-dinitrophenylhydrazones and/or semicarbazones (mixed m. p.). All other solid materials were also identified by mixed m. p. Ethylene, propene, and acetylene in unsaturated hydrocarbon fractions were estimated individually in some runs, by Hurd and Spence's method (*J. Amer. Chem. Soc.*, 1929, **51**, 3353). The normal chemical examination of pyrolysate fractions was in many cases supplemented by infrared spectrometry.

Tables 1 and 3 summarise the experimental conditions for 13 runs. They show the amount of liquid pyrolysate (*a*) from each, and the amount and composition of the final gaseous pyrolysate (*b*) collected in the receiver; all gas analyses are reported on a nitrogen-free basis. Details of the examination of (*a*) are given separately below for each pyrolysis.

Ethylene Dibenzoate (III).—Ethylene glycol was benzoylated in acetone solution, and the product precipitated with alkali. Recrystallisation (benzene) gave pure (III), m. p. 72—73° (lit. 73°).

Pyrolysis 1 (*vessel P.1*). Distillation of (*a*) yielded (i) benzene (2·5 g.; characterised as *m*-dinitrobenzene), (ii) a fraction, b. p. 202—203°/760 mm. (14·5 g.), consisting of (VII) (52%: infrared spectrum; saponified to sodium benzoate and an acetaldehyde resin), acetophenone (38%), and benzoic acid (10%), and (iii) benzoic acid (17 g.).

Pyrolysis 2 (*vessel P.2*). A trace of acetaldehyde collected in the cold trap. Distillation of (*a*) removed 12 g. of liquid; the residue, freed from benzoic acid by alkali, was extracted with cold ethanol, and the filtrate evaporated (cold) in a current of air. The final residue became blue, indicating an acid anhydride, on treatment with (*p*-nitrobenzamido)phenylacetic acid (Davidson and Newman, *loc. cit.*), and was identified (infrared spectrum) as benzoic anhydride.

Vinyl Benzoate (VII).—Prepared as described in B.P. 581,501/1946 (b. p. 203°/760 mm., 72—74°/3 mm.), various batches were found to contain between 2% and 7% of acetophenone (Iddles and Jackson's method, *loc. cit.*). This was allowed for in calculating the additional ketone produced on pyrolysis.

TABLE 1. *Pyrolysis of ethylene dibenzoate, vinyl benzoate, and benzoylacetaldehyde.*

	Ethylene dibenzoate		Vinyl benzoate			Benzoyl-acetaldehyde	
Pyrolysis No.	1	2	3	4	5	6	7
Reaction vessel	P.1	P.2	P.1	P.2	P.1 *	P.1	P.2
Temp.	550°	500°	550°	500°	500°	550°	400°
Feed rate (g./min.)	0·40	0·40	0·40	0·27	0·30	0·50	0·33
Weight pyrolysed (g.)	99	50	40	50	40	40	40
(*a*) Liquid pyrolysate (g.)	72	46·5	28	40	26·5	31·5	34
(*b*) Gaseous pyrolysate (l.)	7·5	2·5	8	6	9	5	4
Composition (%) of (*b*):							
Carbon dioxide	†	14·3	20	8·5	13·8	5	2
Carbon monoxide	†	82·1	75	73	64·7	95	97
Hydrogen	—	Nil	Nil	Nil	12·3	Nil	Nil
Methane	—	Nil	Trace?	Trace	6·8	Nil	Nil
Unsat. hydrocarbons (total)	—	3·5	*ca.* 5	18	2·3	Nil	1

* Reaction vessel packed with stainless-steel turnings. † Detected qualitatively. — Not examined.

TABLE 2. *Formation of acetophenone from vinyl benzoate as a function of reaction temperature.*

Reaction vessel	P.2	P.2.	P.2	P.2	P.2	P.1
Feed rate (g./min.)	0·25	0·27	0·30	0·30	0·27	0·40
Temp.	300°	350°	400°	500°	500°	550°
Acetophenone (%, found)	8·0	10·5	16·5	21·8	19·0	26·0
Acetophenone (%, calc.)	7·7	11·3	14·8	21·8	21·8	25·4

Pyrolysis 3 (*vessel P.1*). Distillation of (*a*) yielded (i) benzene (1 g.; characterised as *m*-dinitrobenzene), (ii) a liquid, b. p. 64—110°/40 mm. (15 g.), (iii) a liquid, b. p. 110—130°/40 mm. (1 g.), and (iv) benzoic acid (1 g.). Fractions (ii) and (iii) combined contained 26% (corrected) of acetophenone. No benzaldehyde could be detected in (*a*). The gaseous pyrolysate (*b*) contained acetylene (infrared spectrum), but no keten (aniline–ether trap) or divinyl ether (infrared spectrum).

Pyrolysis 4 (*vessel P.2*). Distillation of (*a*) yielded liquids (i) b. p. 22—66°/4 mm. (2 g.), (ii) b. p. 66—72°/1 mm. (2 g.), (iii) b. p. 72—80°/1 mm. (22 g.), and (iv) b. p. 80°/1 mm. (10 g.). Fractions (i) and (ii) were found (infrared spectrum) to contain (VII), acetophenone, and much styrene; (iii) contained the same constituents, but with less of styrene; (iv) contained benzoic acid. The acetophenone content of (*a*) was 19% (corrected); there was no benzaldehyde. The gaseous pyrolysate (*b*) contained ethylene and acetylene (infrared spectrum), but no keten (aniline–ether trap).

Pyrolysis 5 (*over stainless steel*). For this run only, the vessel P.1. was packed with stainless-steel turnings instead of Pyrex-glass helices. No benzaldehyde could be detected in (*a*), which was not otherwise examined; keten was absent from the exit gases. A heavy carbonised deposit formed in the reaction vessel.

The acetophenone content of the pyrolysate from six different runs (including four not detailed in Table 1) is shown in Table 2; it is approximately related to reaction temperature T, over the range 300—550°, by the linear expression $T = 190 + 14{\cdot}2$ (acetophenone content). This relationship is only very approximate, in view of the slight variation in experimental conditions.

Benzoylacetaldhyde (VIII). Ethyl formate (1·5 mole) and acetophenone (1 mole) were

treated with sodium ethoxide (0·5 mole) in dry ether (100 g.) as described by von Bülow and Sicherer (*loc. cit.*). The resultant sodium salt was converted into the sparingly soluble copper salt; this was filtered off and washed, and (VIII) was liberated from it by cautious acidification with cold dilute mineral acid. Three separate preparations gave slightly impure (VIII), with concordant analyses [Found: C, 74·3; H, 5·7%; equiv. (alkaline hydrolysis), 175. Calc. for $C_9H_8O_2$: C, 73·0; H, 5·4%; equiv., 148]. It was characterised as its phenylhydrazone (mixture of isomers), m. p. 124—126° (decomp.) (Found: N, 11·9. Calc. for $C_{15}H_{14}ON_2$: N, 11·8%). Von Auwers and Schmidt (*Ber.*, 1925, **58**, 536) quote m. p. 126° (decomp.). Owing to its instability, crude (VIII) could not be further purified by fractionation *in vacuo*; 20—30% of a small batch could be distilled at 94—98°/1 mm. (Found: C, 74·3; H, 5·8%), but thereafter water was liberated during distillation, and at least 33% of the batch became wholly resinified. A small quantity of 1 : 3 : 5-tribenzoylbenzene, m. p. 116—117° (from ethanol), which is a known condensation product of (VIII), separated from the crude (undistilled) ketoaldehyde (Found: C, 83·4; H, 4·8. Calc. for $C_{27}H_{18}O_3$: C, 83·1; H, 4·7%). Claisen (*Annalen*, 1894, **281**, 306) quotes m. p. 118°. Calculations based on the equivalent weight and analytical figures suggest, therefore, that the crude (VIII) is contaminated with 11—13% of this triketone.

Pyrolysis 6 (*vessel P.*1). Distillation of (*a*) yielded (i) acetophenone, b. p. 110—116°/55 mm. (27 g.; infrared spectrum), and (ii) a tarry residue (3—4 g.).

Pyrolysis 7 (*vessel P.*2). Distillation of (*a*) yielded (i) acetophenone, b. p. 58—70°/3 mm. (15·5 g.), (ii) a liquid, b. p. 90—100°/3 mm. (6·5 g.) consisting of (VIII) together with a little acetophenone (infrared spectrum), and (iii) a brown resin (12 g.).

TABLE 3. *Pyrolysis of vinyl acetate and* iso*butyrate.*

	Vinyl acetate					Vinyl *iso*-butyrate
Pyrolysis No.	8	9	10	11	12	13
Reaction vessel	P.1	P.1	S	S	V	P.3
Temp.	550°	550°	500°	500°	550°	550°
Feed rate (g./min.)	0·15	0·16	0·57	0·76	0·34	0·08
Weight pyrolysed (g.)	82	85·8	102	91·1	86	9·2
(*a*) Liquid pyrolysate (g.)	49·5	60·6	13·9	13·8	54	5·6
(*b*) Gaseous pyrolysate (l.)	10·2	13·4	94·5	58	25·6	2·1
Composition (%) of (*b*):						
Carbon dioxide	4·1	3·3	2·6	7·5	3·2	2·4
Carbon monoxide	84·2	88	39·4	36	81·7	67·5
Hydrogen	Nil	Nil	46·1	45	Nil	Nil
Methane	5·1	5	11·5	10	8·2	18·9
(*c*) Unsat. hydrocarbons (total)	4·6	3·7	0·4	0·8	6·9	11·2
Approx. molar ratio of unsat. hydrocarbons in (*c*):						
Ethylene	0·6	—	—	—	0·4	0·8
Propene	0·1	—	—	—	0·1	0·1
Acetylene	0·3	—	—	—	0·5	0·1

Vinyl acetate (IX; R = R′ = H). Redistilled commercial ester (*ex* Shawinigan Ltd.) was used.

Pyrolysis at 420° *and* 700° (*vessel P.*1). Preliminary runs established the optimum temperature at *ca.* 550°, and showed that virtually no decomposition occurs at 420°, while at 700° strong secondary decompositions occur. For example, at 700°, propene disappears from the pyrolysate, and the methane content of (*b*) rises to *ca.* 25%, owing to more complete breakdown of acetaldehyde, and, to a lesser extent, of propene (cf. Hurd, *op. cit.*, pp. 236 and 77, respectively).

Pyrolyses 8 *and* 9 (*vessel P.*1). These two runs show that reasonably reproducible results can be obtained (Table 3). The two liquid pyrolysates (*a*) were combined; distillation yielded (i) a volatile fraction, b. p. 20°/660 mm. (mainly acetaldehyde), (ii) a colourless liquid, b. p. 52—60°/760 mm. (mainly acetone), (iii) a yellowish liquid, b. p. 62—87°/760 mm. [mainly recovered (IX), *ca.* 22% of weight pyrolysed: unsaturated; polymerised on heating with benzoyl peroxide], and (iv) a cloudy yellow liquid, b. p. 97—114°/760 mm. (mainly acetic acid containing some acetic anhydride: infrared spectrum). The exit gases contained keten (acetanilide from aniline–ether trap), ethylene, propene, and acetylene (infrared spectrum), but no divinyl ether (infrared spectrum).

Pyrolyses 10 *and* 11 (*vessel S*). These duplicate runs again show reasonable reproducibility (Table 3). The liquid pyrolysates (*a*) contained traces of water (anhydrous $CuSO_4$ test); keten was absent from the gaseous pyrolysates (*b*).

Pyrolysis 12 (*vessel V*). Qualitatively, the results were the same as those of runs 8 and 9, but the ratio between the reaction routes was somewhat altered (Table 4). High accuracy is not claimed for the ratios summarised in Table 4, since certain products (*e.g.*, ethylene) cannot yet be accounted for; but approximate figures have been reached by correlating the analyses of gas (*b*) with the weight of the fractions obtained from liquid (*a*).

Vinyl iso*butyrate* (IX; R = R′ = Me). The ester, prepared from vinyl acetate and *iso*butyric acid by ester interchange (cf. Burnett and Wright, *Trans. Faraday Soc.*, 1953, **49**, 1108), had b. p. 105°/760 mm. It was briefly described in B.P. 585,396/1947 and U.S.P. 2,460,105/1949, but no physical constants were quoted.

Pyrolysis 13 (*vessel P.3*). The smallest reaction vessel was used because of the small quantity of ester available; and the entire liquid pyrolysate was collected directly in the cold trap. Distillation of (*a*) yielded (i) a volatile fraction, b. p. 20°/660 mm. (mainly acetaldehyde), (ii) a

TABLE 4. *Ratios between reaction routes in pyrolysis of vinyl acetate and* iso*butyrate* (*Temp.* 550°).

Pyrolysis No.	Reaction vessel	Ester	Route-ratio (molar) A^2	B^1	C^2	R/C^1
8–9 (av.)	P.1	Acetate	0·03	0·47	0·03	0·47
12	V	,,	0·11	0·15	0·01	0·73
13	P.3	*iso*Butyrate	0·06	0·30	0·01	0·63

colourless liquid, b. p. 92—100°/760 mm. (mainly methyl *iso*propyl ketone), (iii) a colourless liquid, b. p. 102—108°/760 mm. [mainly unchanged (IX), *ca.* 7% of weight pyrolysed: infrared spectrum], and (iv) a brownish liquid, b. p. 145—165°/760 mm. (mainly *iso*butyric acid, containing no *iso*butyric anhydride: infrared spectrum). In addition to the three main components of the gaseous pyrolysate (*b*) listed in Table 3, the following three components were identified by the infrared spectrum: **2 : 3**-dimethylbut-2-ene [bands at 1450 (s), 1390 (s), 1162 (s) cm.$^{-1}$], 2-methylbut-1-ene [892 (w) cm.$^{-1}$], and 2-methylbut-2-ene [804 (s) cm.$^{-1}$]. 3-Methylbut-1-ene could not be identified positively.

New Infrared Data.—The gaseous pyrolysate (*b*) from runs 4, 8, 9, and 2 showed a strong band at 1140 cm.$^{-1}$ which still remains unassigned. The spectra of the following substances were measured, and do not appear to have been recorded previously: Benzoic anhydride [1787 (s), 1736 (m), 1620 (w), 1463 (w), 1210 (s), 1160 (m), 1035, 1010, 985 (triplet: s) cm.$^{-1}$]; **1 : 3 : 5**-tribenzoylbenzene [1652 (broad: s), 1555 (broad: s), 1239 (w) cm.$^{-1}$]; vinyl *iso*butyrate [875 (w), 962 (w), 1103 (w), 1167 (m), 1209 (w), 1675 (w), 1795 (m) cm.$^{-1}$]; vinyl benzoate [706 (w), 870 (w), 952 (w), 1028 (w), 1075 (m), 1100 (m), 1140 (s), 1260 (s), 1605 (w), 1650 (w), 1730 (m) cm.$^{-1}$].

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Exchange Reactions of Solid Oxides. Part VI. The Reactions of Carbon Monoxide, Carbon Dioxide, and Oxygen on Cuprous Oxide, Nickel Oxide, and Chromium Oxide.*

By E. R. S. Winter.

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The reaction $2CO + O_2 \longrightarrow 2CO_2$ has been studied by using mainly the stoicheiometric mixture of reactants, on NiO, Cr_2O_3, and Cu_2O at pressures of 1—9 cm. and temperatures from 10° to 155°. On the first two oxides the reaction proceeds with an apparent E of 5·5 kcal. mole^{-1} and zero respectively, following the rate law $dP_{CO_2}/dt = kP_{CO}/(P_{CO} + P_{CO_2})$. By using ^{18}O it has been shown that the reaction probably proceeds on only a small fraction (<2·5%) of the surface oxygen sites by an extraction reaction, the carbon monoxide removing a surface oxygen ion which is rapidly replaced by oxygen from the gas phase: evidence is reviewed which suggests that on these two oxides the rate-determining step is the latter, namely, $O_2(gas) + (e_s/\square^-_s)$ † $\longrightarrow O^{2-}_{(s)} + O_{ads}$. The oxygen exchange of these three gases with the surface oxygen ions is negligible at temperatures of interest in the oxidation studies.

The oxidation reaction on Cu_2O (formed on precipitated copper powder) probably proceeds by the same mechanism. Here ready exchange of oxygen occurs between the two oxides of carbon and the surface oxygen ions of the catalyst. The oxidation reaction on Cu_2O has an apparent E of 10 ± 2, and the exchange reactions with carbon monoxide and dioxide have E about 10 and 4 kcal. mole^{-1} respectively. The oxidation proceeds on 10—40% of the surface sites, the proportion increasing with rising reaction temperature. By using both ^{13}C and ^{18}O it has been shown that no exchange of carbon occurs between carbon monoxide and carbon dioxide on the catalyst surface.

Garner and his co-workers (*Proc. Roy. Soc.*, **1949**, *A*, **197**, 294; **1952**, *A*, **211**, 472; *Discuss. Faraday Soc.*, **1950**, **8**, 246) have recently investigated extensively the interactions of various gases (especially oxygen, carbon monoxide, and carbon dioxide) with cuprous oxide and cupric oxide. The techniques used included measurement of heats and rates of adsorption and of semiconductivity, upon oxide films and granular oxide prepared by oxidation of the metal. It appears that this work was necessarily performed at gas pressures of less than 3 mm., and mostly less than 0·1 mm., pressures which are often of little practical interest in the study and application of heterogeneous catalysis. In addition, although new and valuable data have been obtained which have led to significant theoretical advances, the details of the interactions are not established: similar remarks apply to the interactions of the same three gases on nickel oxide, which have been studied recently in a similar fashion by Dell and Stone (*Trans. Faraday Soc.*, 1954, **50**, 501) and from a kinetic viewpoint at higher pressures by Parravano (*J. Amer. Chem. Soc.*, 1953, **75**, 1448).

In an attempt to clarify the position and to provide further information, these systems have been examined with ^{18}O and ^{13}C as tracers: also the catalysed oxidation, $2CO + O_2 \longrightarrow 2CO_2$, has been studied on the two oxides, the mass spectrometer being used to follow the course of the reaction. A similar investigation, with chromium oxide as catalyst, is also reported here. Pressures of 1—9 cm. were used.

Experimental

Materials.—Cuprous oxide was prepared by controlled oxidation of pure copper (Winter, *J.*, 1954, 3342), nickel oxide by heating "AnalaR" nickel carbonate in air at 870° for 24 hr., and chromium oxide by controlled decomposition of "AnalaR" chromic oxide (Bevan, Shelton, and Anderson, *J.*, 1948, 1729).

Oxygen containing 30% of ^{18}O was obtained by thermal diffusion (Winter, *loc. cit.*). Carbon monoxide containing *ca.* 60% of ^{13}C was obtained from A.E.R.E., Harwell. Normal carbon

* Part V, *J.*, 1954, 1522. † For symbolism, see p. 2734.

monoxide was made by the action of concentrated sulphuric acid on 98% "AnalaR" formic acid; both liquids were thoroughly outgassed before reaction and the product was repeatedly fractionated *in vacuo* until mass spectrometric examination of the final material revealed no detectable impurity at mass **44** or **32**. Carbon dioxide containing *ca.* 60% of ^{13}C was made by oxidising ^{13}CO with a slight excess of normal oxygen on a heated platinum filament and fractionating the product *in vacuo*. Normal carbon dioxide was prepared by fractionating the commercial solid *in vacuo*.

Method.—The reactions were followed by the technique employed for studying the isotopic exchange reactions of solid oxides (Winter, *J.*, 1950, 1170): *i.e.*, the oxide, suitably pre-treated (see below), was confined in a Pyrex or Hysil reaction vessel provided with a small leak to the ionisation chamber of the mass spectrometer; on admission of the reactant gas the relevant mass peaks were continuously monitored. Thus the reaction system was essentially static, but no evidence was found that gas-phase diffusion was a rate-limiting factor (cf. Houghton and Winter, *J.*, 1954, 1509). The volume of the reaction system varied between 30 and 80 ml. The mass spectrometer and auxiliary apparatus have been briefly described by Winter (*J.*, 1954, 1522). For work on Cu–Cu_2O two samples, A and B, each of 4 g., were used, the oxide film being first formed to a depth of *ca.* 50 Å with normal oxygen, with four cycles of alternate oxidation and reduction (cf. Garner, Gray, and Stone, *Proc. Roy. Soc.*, 1949, *A*, **197**, 294); at the end of the work the B.E.T. surface areas of the samples, determined with nitrogen at −193°, were 2·21 and 0·62 m.^{2} g.$^{-1}$ respectively, an area of 16·2 Å^2 being used for the nitrogen molecule. The experiments were performed in groups, in roughly the order given below, with after-treatment with enriched oxygen as noted: no particular precautions were taken to exclude grease or mercury vapour from the catalyst. Similar remarks apply to NiO, the same 1 g. sample being used for all the work, except in the experiments on $Ni^{18}O$: the B.E.T. (N_2) surface area was 5·48 m.^{2} g.$^{-1}$. For Cr_2O_3 the B.E.T. (N_2) area was 14·2 m.^{2} g.$^{-1}$; the same 1 g. sample was used throughout the work.

Cuprous Oxide—Sample A. (*a*) Exchange reactions of carbon dioxide. The oxide was held at 38° in the presence of 1 cm. of a 1 : 1 mixture of normal oxygen and oxygen containing 30% of ^{18}O, and 1·7 cm. of normal carbon dioxide was then added to the system. In 26 min. the ^{18}O content of the carbon dioxide had risen smoothly to 1·65% but there was no change in the 32 : 34 : 36 mass ratios of the oxygen present. The temperature was rapidly raised to 61°; the rate of exchange of the carbon dioxide increased but again no change occurred in the oxygen mass ratios, although now oxygen was being lost from the gas phase, doubtless owing to oxidation of the underlying copper: the rate of oxygen loss was negligible at 38°. A material balance showed that at 61° the amount of ^{18}O gained by the carbon dioxide was approximately equal to the amount transferred to the oxide surface by oxidation during the experiment.

The exchange of carbon dioxide with an oxygenated surface was then followed at three temperatures, at a pressure of 3·8 cm. The gas was pumped out after each run, *ca.* 3 cm. of 15% ^{18}O were admitted at the reaction temperature, and the whole was left for 30 min.; the oxygen was removed by a Töpler pump and finally the oxide was treated at 76° overnight with 2 mm. of oxygen containing 15% of ^{18}O. In the morning the pressure in the reaction vessel was apparently $\ll 10^{-1}$ mm.; vigorous pumping was applied for 10 min. and the vessel cooled, with continued pumping, to the reaction temperature: pumping was continued for at least 1 hr. in each case. The carbon dioxide was then added and the 44/46 peaks were monitored until equilibrium was reached: the equilibrium ^{18}O content was about 1%. These three runs gave good first-order plots. On the assumption that the pre-treatment with enriched oxygen gave a surface containing 15% of ^{18}O in each case, the values of k_0* and n_s* were calculated, the volume of gas used being known: a plot of log $k_0 n_s$ *versus* $10^3/T$ gives an apparent activation energy of 4·7 ± 1·0 kcal. mole^{-1}. The results are given in Table 1; the pressure-dependence was not investigated.

It might be argued that the observed exchange is due to reaction with adsorbed oxygen atoms or molecules not removed by reaction with the underlying metal overnight or by the subsequent pumping. To test this, at the conclusion of all the work below on Cu–Cu_2O the above experiment was repeated at 38° with, however, a pre-treatment temperature of 155° (at which the 2 mm. of enriched oxygen was removed from the gas phase in less than 2 min.): no free oxygen should be present the next morning under these conditions, but essentially the same kinetics were observed as before.

(*b*) Exchange reactions of carbon monoxide. The exchange of ^{18}O between the oxygenated

* The symbols are those used earlier in this series (cf. Houghton and Winter, *loc. cit.*).

surface and 6 cm. of normal carbon monoxide was followed similarly, by using the same procedure to regenerate the ^{18}O content of the oxide surface between each kinetic run. The results are summarised in Table 1; good first-order plots were obtained: the values of log k_0n_s yield $E = 11{\cdot}5 \pm 2{\cdot}0$ kcal. mole^{-1}. As with carbon dioxide, a later run at 38° in which the pre-

TABLE 1.

Exchange with	$10^5/T$	$10^{-13}n_s$*	$\log_{10} k_0n_s$	Exchange with	$10^5/T$	$10^{-13}n_s$*	$\log_{10} k_0n_s$
	Sample A				*Sample B*		
CO_2 at 3·8 cm.	272·5	3·04	17·655	CO_2 at 4·2 cm. ...	329·0	1·96	17·159
	295·9	2·40	17·390		329·0	2·05	17·149
	311·5	1·97	17·250		351·0	1·36	17·018
CO at 6 cm.	295·9	3·78	17·558		351·0	1·25	17·000
	312·5	2·48	17·114	CO at 5·7 cm.	300·3	1·50	17·620
	341·4	1·68	16·437		304·2	1·44	17·600
					317·4	1·30	17·485
					329·0	0·95	17·150
					343·6	0·89	17·060

* n_s = atoms g.$^{-1}$.

treatment with ^{18}O was carried out at 155° gave essentially the same rates as those shown in Table 1.

While the exchange with carbon monoxide was being investigated, the rate of production of carbon dioxide was measured by observing the rate of increase of the peak at mass 44. Two

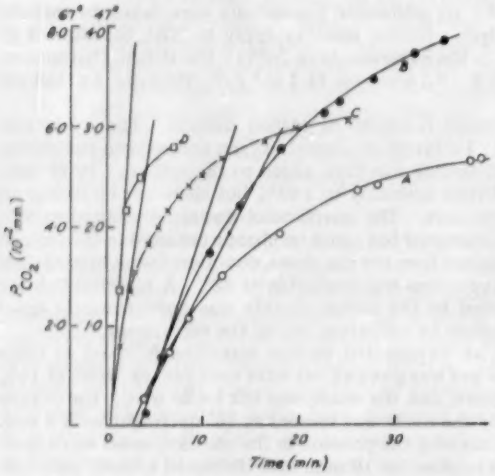


FIG. 1. *Formation of carbon dioxide from carbon monoxide on* Cu_2O *during the exchange reaction at* P_{CO} 6·0 *cm. and* (*A*) 47°, (*B*) 67°. *Also formation of carbon dioxide from* $(CO)_{ads}$ *on admission of oxygen to catalyst at* P_{O_2} 2·0 *cm. and* (*C*) 46°, (*D*) 67°.

experiments are shown in Fig. 1, and the initial rates of formation of carbon dioxide give $E \approx 14$ kcal. mole^{-1}. The rate of formation of carbon dioxide on admission of oxygen to the freshly-evacuated surface within 3 min. of the completion of an exchange reaction was measured in two cases: these experiments are also shown in Fig. 1 and yield $E \approx 17$ kcal. mole^{-1} from the initial rates of reaction. It appears from the above experiments that the rate of formation of carbon dioxide by reaction between the oxygenated surface and adsorbed monoxide is slow; thus a pressure of less than 1/30 mm. is produced (in the presence of ~6 cm. of carbon monoxide) at 47° in 40 min.; nevertheless it might be argued that the observed exchange is due, not to a direct exchange of oxygen of the carbon monoxide with surface oxygen, but to exchange of oxygen between $CO_{(ads)}$ and $CO_{2(ads)}$, only the latter species being exchanged directly with surface oxygen. To test this a mixture of 6·5 cm. of normal carbon monoxide and 1·3 cm. of carbon dioxide containing *ca.* 60% of ^{13}C and *ca.* 3% of ^{18}O was introduced into the reaction vessel, the catalyst having been previously exposed to *ca.* 15% of ^{18}O as usual. Both the gases picked up ^{18}O slowly from the surface, but no ^{13}C appeared in the carbon monoxide: this experiment was performed at 18°, 47°, and 68°, and the observations in each case were continued for an hour. It should be noted that introduction of $^{13}CO_2$ into the mass spectrometer produced an *immediate* significant increase in the mass 28 and 29 tube residuals, and a change in their ratio:

this effect became steady in 1—2 min. and is ascribed to CO^+ fragments produced from the carbon dioxide under the relatively high electron-accelerating potential used in the mass spectrometer ion source between filament and trap. (CO^+ is produced from CO_2 by electron bombardment with an accelerating potential of about 20·4 v, according to Stueckelberg and Smyth, *Phys. Rev.*, 1930, **36**, 472; see also Kallmann and Rozen, *Z. Physik*, 1929, **58**, 52; 1930, **61**, 61; Morrison, *J. Chem. Phys.*, 1954, **22**, 1219.) This effect was allowed for in interpreting these three

FIG. 2. *Reaction,* $2CO + O_2 \longrightarrow 2CO_2$, *on* Cu_2O (*stoicheiometric mixture*). *A*, P_T 3·1 *cm.*, 86°; *B*, P_T 2·5 *cm.*, 66°; *C*, P_T 3·3 *cm.*, 48°.

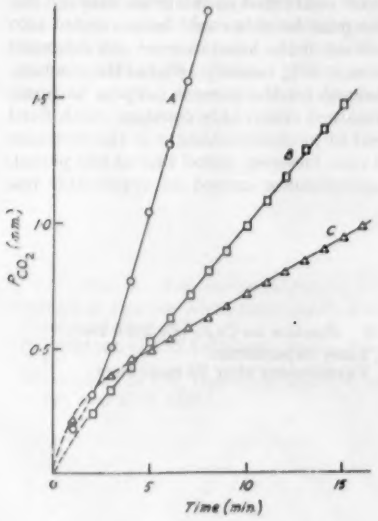
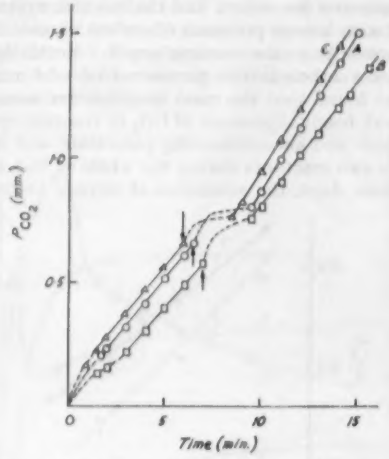
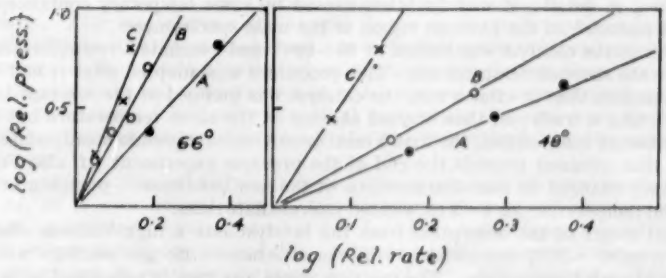


FIG. 3. *Reaction,* $2CO + O_2 \longrightarrow 2CO_2$, *on* Cu_2O; *initially the stoicheiometric mixture; addition of oxygen or carbon dioxide after 6—7 minutes, as indicated by arrows.*



Curve	Initial P_T (cm.)	Final P_{O_2} (cm.)	P_{CO} (cm.)
A	2·5	0·83	4·57
B	3·1	1·8	2·1
C	3·3	6·9	2·2

FIG. 4. *Reaction on* Cu_2O *at 48° and 66°.*



A, P_T; *B*, P_{CO}; *C*, P_{O_2}.

experiments; the main proof that no reversible formation of ^{13}CO occurred was that after the first 1—2 min. the 28 : 29 ratio remained constant for the remainder of the experiment at a value corresponding to only some 3% of ^{12}C while the 44 : 45 ratio was constant throughout. A more direct proof would be to isolate the carbon monoxide and analyse it separately.

(*c*) The oxidation of carbon monoxide by oxygen. A study was made of the reaction $2CO + O_2 \longrightarrow 2CO_2$, catalysed by the Cu–$Cu_2O$ surface, by following the rate of appearance of mass 44 in the sample bled into the mass spectrometer. The reaction was carried out under static conditions in the same apparatus, and in general the stoicheiometric mixture of reactants

was used but in some reactions, once a steady state had been reached, more of one of the reactants was injected into the system and the new steady state determined. In general the value of dP/dt (where P = pressure of carbon dioxide in the system) became constant in the first 2—4 min. and remained so for at least a further 10 min.: this steady value was used in calculating the rate constant. Normally only the initial stages of the reaction were followed, *i.e.*, the first 10—15 min. of the reaction, or the corresponding time after the change of gas composition by injection of more of one of the reactants. Some typical experiments are shown in Figs. 2 and 3, and the results are summarised in Figs. 4 and 5. It is seen from Fig. 5 that the surface gradually became more reactive with use, the rate nearly doubling, at any given temperature, during 20 experiments, while the apparent activation energy fell from 11·5 to ~9·0 kcal. mole^{-1}. We shall assume in the Discussion that $E = 10 \pm 2{\cdot}0$ kcal. mole^{-1}. The mass spectrometer ion source and the reaction system leak were calibrated at intervals through the work with known pressures of carbon dioxide so that the peak heights could be converted into gas pressures in the reaction vessel. Normally observations of the kinetics were not extended beyond a carbon dioxide pressure of 1·5—2·0 mm., *i.e.*, at most 20% (usually 10%) of the reaction. It was found that the mass spectrometer sensitivity, defined for the present purpose as (mass 44 peak height)/(pressure of CO_2 in reaction system), remained reasonably constant (with fixed electron- and ion-accelerating potentials) and independent of moderate changes in the pressures of the two reactants during the whole of this work. It was, however, noted that at one period, for some days, the admission of oxygen to the mass spectrometer caused an appreciable rise

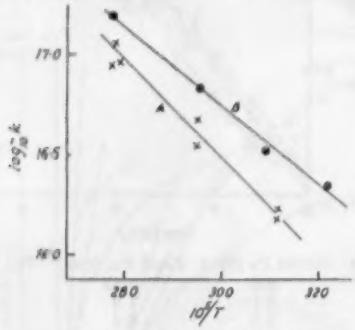


FIG. 5. *Reaction on* Cu_2O ($P_T \approx 3{\cdot}0$ *cm.*).
A, Early experiments.
B, Experiments after 20 more runs.

in the mass 44 tube blank: this produced an anomalous rapid rise of the mass 44 peak at the beginning of a reaction but did not alter the steady-state value of dP_{CO_2}/dt. This phenomenon was not studied in detail: it was doubtless caused by some temporary contamination, with carbonaceous material, of the filament region of the mass spectrometer.

After each run the catalyst was heated to 96—100°, and evacuated overnight, then isolated and cooled to the reaction temperature. This procedure was adopted after it had been noted on several occasions that if, after a run, the catalyst was pumped at the reactant temperature for *ca.* 5 min. and a fresh run then started at once at the same temperature but with a gas mixture of different composition, the first 5 min. or so yielded a pseudo-steady state which was the same as that attained towards the end of the previous experiment (cf. also Fig. 3): this false rate slowly changed to that characteristic of the new conditions: pumping between runs at the reaction temperature for 1—2 hr. yielded intermediate rates.

The initial stages of the desorption from the catalyst into a high vacuum after a kinetic experiment (run to ~20% completion) with the stoicheiometric gas mixture was examined qualitatively at each temperature. The reaction vessel was rapidly evacuated to *ca.* 10^{-3} mm., through the auxiliary vacuum line, and the gas then being evolved from the catalyst was diverted *directly* into the mass spectrometer ion source by means of a tap by-passing the leak. The mass spectrometer showed a small transitory peak at mass 32 which very rapidly dropped to zero (*i.e.*, to the level of the tube residual) but peaks at mass 44 and 28 remained more or less steady at high values for many minutes at all temperatures. The peak at mass 28 was too large to have been caused solely by CO^+ fragments formed from the carbon dioxide molecules in the ionisation process; this was confirmed by following the desorption of masses 28 and 30 after 30% ^{18}O had reacted with normal carbon monoxide.

The effect of pre-treating the surface was studied at 50°: the catalyst was outgassed overnight at 96—100°, isolated, cooled to 50°, exposed to 1 cm. of carbon dioxide for 15 min., and

pumped hard for 5 min.; the reaction mixture (3·0 cm.) was then added and the production of carbon dioxide followed as usual. Similar experiments were performed in which pre-treatment was with carbon monoxide and oxygen. Pre-treatments with carbon monoxide and carbon dioxide caused no change in the velocity of the subsequent oxidation reaction, but treatment with oxygen caused the rate during the first 4 min. to be about 3 times that on the untreated catalyst. The run with oxygen pre-treatment showed marked curvature of the P_{CO_2}–time plot after the eighth minute, probably because of exhaustion of the reaction mixture, since the reaction was by then more than 30% complete.

(*d*) The oxidation reaction on an ^{18}O-enriched surface. After the above work the sample was outgassed at 155° for 3 hr. and *ca.* 0·64 ml. (N.T.P.) of 30% ^{18}O added: this was apparently all taken up in less than 2 min. The catalyst was left isolated at 155° overnight to ensure so far as possible the complete utilisation of the oxygen and cooled to 48°. The oxidation reaction was then carried out, at an initial pressure of 2·7 cm. of the stoicheiometric mixture made from isotopically normal gases; and the mass 44, 46, 28, and 30 peaks were monitored. A similar experiment was performed in which the reaction was carried out at 155° with 2·2 cm. of the normal reaction mixture; the two runs are summarised in Fig. 6.

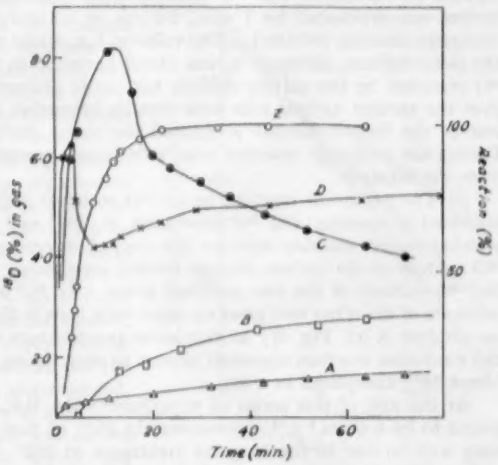


FIG. 6. *Reaction on* $Cu_2{}^{18}O$.
Extent of reaction (right-hand scale), *A* at 48°, and *E* at 155°.
^{18}O content of CO (left-hand scale), *B* at 48°.
^{18}O content of CO_2 (left-hand scale), *C* at 48°, and *D* at 155°.

Sample B. After the above work sample A was accidentally spoilt. It appeared from discussions with Dr. F. S. Stone that there was some risk of the observations' being influenced by the presence on the surface of active adsorbed oxygen (cf. Garner, Gray, and Stone, *loc. cit.*) owing to the relatively low temperatures at which the oxide was outgassed and treated with ^{18}O between experiments. The more important parts of the ^{18}O work were therefore repeated, with a higher outgassing temperature, on a fresh catalyst prepared from the same bulk batch of metallic copper.

(*a*) Exchange reaction of carbon dioxide. The fresh catalyst (previously oxidised to a depth of *ca.* 50 Å with normal oxygen, following several cycles of alternate oxidation and reduction as for sample A) was outgassed at 200° for 24 hr., isolated, and treated with *ca.* 1·5 ml. (N.T.P.) of oxygen containing 30% of ^{18}O. After 24 hr. the system was evacuated for 5 min., isolated, and cooled to room temperature during 24 hr.: this procedure of outgassing, ^{18}O treatment, etc., at 200° was carried out between each run.

The exchange reaction was followed at a pressure of *ca.* 4·2 cm. of normal carbon dioxide in the reaction vessel; the first two runs on the new catalyst were anomalously fast, but subsequent experiments were reproducible and are summarised in Table 1; good first-order plots were obtained. Values of k_0 and n_s were calculated by assuming that the surface oxygen ions contained 30% ^{18}O; a plot of $\log k_0 n_s$ yields $E = 3{\cdot}0$ kcal. mole^{-1}.

(*b*) Exchange reaction of carbon monoxide. This was studied in the same way with the same pre-treatment procedure; pressures of 5·5—6·0 cm. of normal carbon monoxide were employed. The results are given in Table 1 and yield $E \approx 9{\cdot}0 \pm 2$ kcal. mole^{-1}. During these experiments the rate of formation of carbon dioxide in the reaction system was followed by noting

the height of the mass 44 peak from time to time. At temperatures between 12° and 20° the rate was negligible, but at 41° and at 60° it was several times that found on catalyst A: these two runs gave linear plots of P_{CO_2} *versus* time, from the slopes of which an apparent activation energy of 21 kcal. mole^{-1} was obtained.

The effect of active adsorbed oxygen was demonstrated by an experiment in which the catalyst, after being outgassed at 200°, was cooled to 76° and then treated with *ca.* 1·2 ml. (N.T.P.) of 30% ^{18}O and left at 76° for 22 hr.; then the system was evacuated for a short time and the catalyst isolated and cooled to 31° during 24 hr. An exchange reaction with normal carbon monoxide at 5·6 cm. was then performed and at the same time the production of carbon dioxide was followed: the system (reaction volume *ca.* 45 ml.) yielded *ca.* 0·85 cm. pressure of carbon dioxide in 41 min.—a much higher rate of production than was found at 60° on the catalyst treated with oxygen at 200°. This exchange reaction had a k_0n_s about 25% and n_s about twice as great as those for the corresponding reaction on the catalyst treated at 200°.

The influence was studied of pre-adsorbed carbon dioxide on the exchange reaction between the surface and carbon monoxide. After the normal outgassing and ^{18}O treatment at 200° the catalyst was cooled to 31° during 24 hr. and then exposed to 0·8 cm. of normal carbon dioxide for 55 min.: the ^{18}O content of the carbon dioxide at this point was noted. The system was evacuated for 1 min., 5·5 cm. of normal carbon monoxide were admitted, and the exchange reaction followed. The value of k_0n_s found was about 25% of that for the reaction on the clean surface, although n_s was about normal: in the calculations it was assumed that the ^{18}O removed by the carbon dioxide had come uniformly from the cuprous oxide surface, *i.e.*, that the surface oxygen ions were equally accessible to both gases; but if the amount of ^{18}O lost to the carbon dioxide is ignored the above statements regarding k_0n_s and n_s still hold. During the exchange reaction relatively large amounts of carbon dioxide were slowly evolved from the catalyst.

(*c*) The oxidation reaction on an ^{18}O-enriched surface. The catalyst was subjected to the standard outgassing and ^{18}O treatment at 200° and cooled to 15°. The isotopically normal stoicheiometric reaction mixture (2·0 cm.) of oxygen and carbon monoxide was added and the ^{18}O content of the carbon dioxide formed monitored; at the same time a record was taken of the ^{18}O content of the two reactant gases. No ^{18}O was taken up by the oxygen, but the ^{18}O contents of the other two gases changed with time in the same manner as in the two experiments on catalyst A (cf. Fig. 6); at this lower temperature the whole process was slower, and indeed the oxidation reaction appeared almost to stop, being some 50% completed in 1½ hr. and only about 70% completed in 4 hr.

At the end of this series of experiments the B.E.T. (N_2) surface area of the catalyst was found to be 0·62 m.^{2} g.$^{-1}$, approximately 25% of that found for catalyst A. This lower value may well be due to the frequent treatment at 200°, but it is nevertheless interesting that k_0 and n_s for both catalysts were similar (cf. Table 1).

TABLE 2. *Reaction* $2CO + O_2 \longrightarrow 2CO_2$ *on* NiO.

$10^3/T$	$\log_{10} k$	P_T *	$10^3/T$	$\log_{10} k$	P_T *	$10^3/T$	P_{O_2}	P_{CO}	k ‡
206·6	1·87 †	1·5	293·2	0·82	3·2	303·1	6·22	1·78	2·72
212·3	1·76 †	1·4	303·1	0·76	3·4	—	—	—	—
220·8	1·675 †	3·3	310·5	0·765 †	2·0	303·1	1·15	2·25	5·74
235·8	1·62 †	2·0	311·5	0·66	3·0	—	—	—	—
285	0·93	3·3	321·5	0·56	3·2	303·1	2·20	4·40	5·64

* Stoicheiometric mixture. † Reaction on $Ni^{18}O$. ‡ Arbitrary units (multiply by $1·77 \times 10^{19}$ to convert k into mole g.$^{-1}$ min.$^{-1}$). Pressures in cm.

Nickel Oxide.—(a) *Oxidation of carbon monoxide by oxygen.* The reaction was studied in the same way as that on $Cu–Cu_2O$, with 1 g. of oxide catalyst. The results are summarised in Table 2, and a few typical experiments are plotted in Fig. 7. Values of log k from Table 2 gave a good Arrhenius plot, with $E = 5·5$ kcal. mole^{-1}. It was found essential to outgas the oxide at 240° for 15 hr. between experiments since, as was proved by direct pumping into the mass spectrometer (cf. above), carbon dioxide was only slowly desorbed from the catalyst and, if not completely removed, acted as a poison.

(b) *Oxidation on an* ^{18}O*-enriched surface.* The oxide was outgassed at 540° for 18 hr., then left for some hours at this temperature in contact with oxygen containing 30% of ^{18}O. The ^{18}O content of the gas was then 5·53% and this figure agreed fairly well with that calculated for complete exchange of the surface oxygen ions of the oxide lattice from data obtained earlier in an examination of the oxygen-exchange reactions of nickel oxide, with oxygen containing

only 1·2% of ^{18}O (Winter, unpublished work) and also with that calculated from the B.E.T. (N_2) surface area of the catalyst. The oxide was cooled in contact with the enriched gas and 1-g. lots were outgassed by pumping overnight at 540°, isolated, and cooled to the required temperature; the stoicheiometric reaction mixture prepared from isotopically normal gases was admitted and the course of the reaction followed; at the end of the reaction the ^{18}O content of the carbon dioxide was determined. From this, knowing the exchangeable surface-oxygen content of

TABLE 3. *The oxygen extraction reaction on* $Ni^{18}O$ and $Cr_2{}^{18}O_3$.

	$Ni^{18}O$				$Cr_2{}^{18}O_3$		
$10^6/T$	206·6	235·8	259·7	310·5	233·6	274·7	315·5
$1 + \log_{10} x$	0·53	0·97	1·16	1·35	1·311	1·182	1·311
x	0·34	0·93	1·46	2·28	2·05	1·52	2·05

x = % of surface oxygen taking part in extraction reaction.

the oxide from the results of the ^{18}O pre-treatment, and also the final pressure of carbon dioxide produced, it was possible to find the fraction, x, of the exchangeable surface-oxygen appearing in the carbon dioxide. These experiments are summarised in Table 3; a pressure of *ca.* 1·3 cm. of the stoicheiometric reaction mixture was used. Insufficient increase in ^{18}O content of the carbon dioxide occurred during the oxidation reaction on $Ni^{18}O$ to make it possible to follow accurately the change of ^{18}O content with time, as was done on $Cu_2{}^{18}O$ (Fig. 6), although it was confirmed that an initial rapid rise took place in ^{18}O content, followed by a slow fall.

After one of the above experiments the 1 g. sample was used as catalyst in ten experiments as recorded in the preceding section (a) at temperatures between 35° and 78°; very small amounts of ^{18}O were picked up by the carbon dioxide in these runs. After the tenth experiment the system was heated to 240° and the carbon dioxide began to take up more ^{18}O—up to 0·4% in 30 min.: the sample was then evacuated and heated, with evacuation, to 525°. After 4 hours' evacuation at this temperature some normal oxygen was added and the uptake of ^{18}O followed. A rapid exchange was observed, the ^{18}O content reaching 1·5% in less than 30 min.

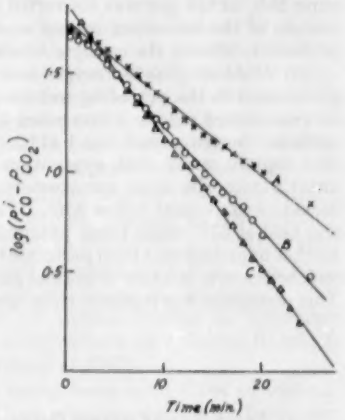


FIG. 7.

(c) *Exchange reactions of carbon dioxide and carbon monoxide.* By using a catalyst surface which had been enriched to ~8% of ^{18}O by exchange with enriched oxygen, it was shown that at temperatures between 30° and 80° the oxygen exchange of these gases with the surface was negligible compared with the rate of oxidation. In another experiment at 57°, with an isotopically normal surface and a reaction mixture prepared from normal carbon monoxide and a 1 : 1 mixture of normal and 30%-^{18}O oxygen, the ^{18}O content of the end product agreed with that calculated from the initial reactants, showing again no appreciable surface exchange (after allowance for the appropriate value of x, cf. Table 3); in addition the 32 : 34 : 36 ratios of the reacting oxygen remained constant for at least 75% of the reaction (after this the peak heights became too small for accurate measurement). The latter observation showed that no reversible adsorption of oxygen as atoms occurred during the oxidation reaction.

Chromium Oxide.—(a) *Oxidation of carbon monoxide by oxygen.* When 1 g. of the oxide was used as catalyst, with outgassing at 535° for *ca.* 15 hr. between runs; the results summarised in Table 4 were obtained. They give $E = 0$.

TABLE 4. *Reaction* $2CO + O_2 \longrightarrow 2CO_2$ *on* Cr_2O_3.

$10^6/T$	233·6	257·8	274·7	315·5
$\log_{10} k$ *	1·888	1·861	1·844	1·905
P_T †	3·0	3·0	2·8	3·0

* Arbitrary units (multiply k by $8·44 \times 10^{16}$ to convert them into mole $g.^{-1}$ $min.^{-1}$). † Stoicheiometric mixtures. Pressures in cm.

(b) *Oxidation on an* ^{18}O*-enriched surface.* The oxide was outgassed at 535° for 18 hr. and then left in contact for 24 hr. at this temperature with 30% ^{18}O. The ^{18}O content of the gas

was then 8·86% and, as for NiO, this figure agreed with that calculated for complete oxygen exchange of the surface ions. The oxide was outgassed for *ca.* 20 hr. at 535°, isolated, and cooled to the reaction temperature, and the ^{18}O appearing in the carbon dioxide formed during the oxidation reaction followed as before: a pressure of 3 cm. of the stoicheiometric reaction mixture was used. As with the other oxides, the ^{18}O content of the carbon dioxide showed an initial rapid rise, followed by a fall as the reaction proceeded. The value of x, the percentage of the exchangeable surface-oxygen transferred to the carbon dioxide, was found as before from the ^{18}O content of the gas at the end of the reaction. The same 1 g. of oxide was then outgassed at 535° overnight, re-treated with 30% ^{18}O, and outgassed again. The oxidation was studied at other temperatures: values of x so found are given in Table 3.

(c) *Exchange reactions of carbon monoxide and carbon dioxide.* No significant exchange with $Cr_2{}^{18}O_3$ (*ca.* 10% of ^{18}O in surface) occurred with either gas in 1½ hr. at temperatures up to 160° (the highest temperature used in experiments reported in the last section was 155°, where the oxidation required some 20 min. under similar pressure). Finally, the oxide with a surface-^{18}O content of *ca.* 4% was exposed to 3 cm. of normal carbon monoxide, and the temperature was slowly raised. After 2 hr. at 130° there was less than 0·4% of ^{18}O in the gas phase; during the next 35 min. the temperature was increased to 250°, extensive reduction of the oxide occurring; some 20% of the gas was converted into carbon dioxide containing *ca.* 2% of ^{18}O, but the ^{18}O content of the remaining carbon monoxide was only about 0·7%. This experiment may have profoundly altered the catalyst which was therefore abandoned.

(d) *Mobility of surface oxygen ions in chromium oxide at 535°.* The last experiment performed as recorded in the preceding section (b) was at 44°; during this the ^{18}O content of the carbon dioxide formed rose to a maximum of over 2·5% and the final value, when all the carbon monoxide had been oxidised, was 1·47%. The oxide was evacuated for 30 min. and the temperature then rapidly raised, with evacuation, to 535°; occasional checks during this time, by pumping directly into the mass spectrometer, showed that the greater part of the adsorbed carbon dioxide was evolved below 250°. The ^{18}O content of this gas remained below 2%. The oxide was held at 535° while being pumped overnight, isolated, and cooled to room temperature. A further oxidation was then performed at this temperature with the same pressure as before of the stoicheiometric mixture of normal gases; the ^{18}O content of the final carbon dioxide was 1·28%. This procedure was repeated twice more; the product of the last run then contained 0·7% of ^{18}O.

Discussion

(a) *Reactions on Cuprous Oxide.*—Garner, Stone, and others (*Proc. Roy. Soc.*, 1949, *A*, **197**, 294; 1952, *A*, **211**, 472; *Discuss. Faraday Soc.*, 1950, **8**, 246) have provided convincing evidence that, at pressures up to about 1 mm. and at temperatures around 25°, both oxygen and carbon monoxide are very readily chemisorbed, the heat of adsorption being 55 kcal. mole^{-1} for oxygen and 20 kcal. mole^{-1} for carbon monoxide. They concluded that on an oxygenated surface at about room temperature $(CO)_{ads}$ forms a "CO_3 complex," formation of which does not involve lattice oxygen; a similar complex is formed by carbon dioxide on an oxygenated surface with a heat of adsorption of about 20 kcal. mole^{-1}. At the temperatures and pressures used they apparently did not regard the formation of the "CO_3 complex" as reversible with respect to carbon monoxide although they showed that in the presence of excess of carbon monoxide it is decomposed to carbon dioxide. The work reported here, showing the ready exchange of oxygen between surface ions and gaseous carbon monoxide and carbon dioxide, may be interpreted by assuming that a $(CO_3)^{2-}{}_{ads}$ complex involving lattice oxygen is readily formed and decomposed under our conditions of higher pressures and that the observed rates of exchange are controlled by the rates of desorption of the gases, with activation energies roughly equal to the heats of adsorption at high coverage:

$$CO + 2O^{2-}{}_{(s)} \rightleftharpoons (CO_3)^{2-}{}_{ads} + (e_2/\square^{-}{}_s)$$

$$CO_2 + O^{2-}{}_{(s)} \rightleftharpoons (CO_3)^{2-}{}_{ads}$$

where $(e_2/\square^{-}{}_s)$ is a surface F′ centre (cf. Rees, "Chemistry of the Defect Solid State," Methuen, 1954, p. 18). This suggestion may be compared with that proposed by Garner

(*J.*, 1947, 1239) for the adsorption of carbon monoxide on oxides of transition elements, where he writes:

$$CO + 2O^{2-} \longrightarrow CO_3^{2-} + 2e$$

or

$$CO + 2O^{2-} + 2M^{2+} \rightleftharpoons CO_3^{2-} + 2M^{+}$$

the two electrons set free being possibly accommodated in the S or D shell of the metal, M.

If we assume that our cuprous oxide surface was energetically very similar to that used by Garner *et al.*, this mechanism requires the heats of adsorption for carbon monoxide and dioxide to decrease at very high coverages to about 10 and 4 kcal. mole^{-1} respectively, these figures being the means of those found by us for the exchange reactions on catalysts A and B; a fall of this magnitude does not appear unreasonable since the coverage of both gases at the pressures used in the heat measurements was certainly less than a half and usually less than one-third of that of oxygen in the same pressure region, and in fact in the case of carbon monoxide Garner, Stone, and Tiley (*Proc. Roy. Soc.*, 1952, *A*, **211**, 472) record a heat of 20·8 kcal. mole^{-1} for 9% coverage, falling to 18·1 at 26% coverage. A linear fall with increasing coverage would, on the basis of these figures, give a value of about 6 kcal. mole^{-1} at saturation. Our experiments, *e.g.*, with ^{13}C, show clearly that, even if the exchange in both cases occurs through the formation of $(CO_3)^{2-}_{ads}$, there is not sufficient disproportionation, *i.e.*, formation of carbon dioxide from carbon monoxide, or the reverse, to account for the rates of exchange found; thus we are forced to the conclusion that, although $(CO_3)^{2-}_{ads}$ when formed may be essentially the same entity in the two cases, its mode of decomposition is governed by the nature of the gas adsorbed. This is possible since formally the formation of the complex involves four electrons from the surface in the case of carbon monoxide but only two in the case of carbon dioxide: we may regard these as being localised in the immediate vicinity of the complex, possibly as defect structures (F′ centres) of limited mobility in sub-surface layers, as suggested in another connection by Rees (*op. cit.*, p. 125). The amount of charge localised near $(CO_3)^{2-}_{ads}$ must determine its mode of decomposition; nevertheless some reduction of the surface does occur, as is shown by the slow formation of gaseous carbon dioxide during the exchange reactions with carbon monoxide (cf. Fig. 1 and similar observations on catalyst B, which should in all cases have been freed from O_{ads} by the treatment at 200°).

Our observations on the oxidation reaction agree in many ways with those of Garner, Stone, and Tiley but exhibit a number of differences. These workers, using a 1 : 1 mixture and a different procedure for attaining a steady surface state, found the rate to be proportional to $P_{O_2}^{1\cdot0}$ and to have $E = 11\cdot4 \pm 2$ kcal. mole^{-1} between 10° and 36°; they found the reaction course to be represented by $\log P_{(2CO+O_2)} = kt$.

It is probable that our experiments, shown in Fig. 1, in which we followed the initial rate of formation of carbon dioxide on admission of oxygen to a catalyst holding adsorbed carbon monoxide, refer to conditions similar to those in the experiments of Garner *et al.* These workers found under their conditions that θ_{CO} was high and θ_O very low, where θ refers to fractional surface coverage: it is likely that the same holds in our experiments. Too much notice should not be taken of our value of 17 kcal. mole^{-1} for E, since it is based on only two runs, and the rate of reaction at 67° was high: the figure may well be in error by at least 3 kcal. mole^{-1}.

The present kinetic work deals only with the initial stage of the reaction, when the rate is linear for an appreciable time, and the rate constants reported are those calculated from the initial rates or from the new steady state after the injection of one or other of the two gases into a reacting mixture which had reached a steady state. It may be noted that in several cases the results obtained by the injection method were confirmed by an experiment in which was employed only gas of the composition of the mixture after injection. The injection technique is not wholly satisfactory but was used since it speeded the work and also because there was a slow drift in reactivity of the catalyst during this study, and it was felt that the method was probably a more accurate way of determining the effect of changing the partial pressures of the two reactants. Fig. 5 shows that the reactivity of the catalyst roughly doubled during the series of experiments, while the activation

energy may have fallen slightly: we conclude that $E = 10 \pm 2$ kcal. mole^{-1} for the stoicheiometric mixture, which is a little lower than that found for the 1 : 1 mixture by Garner *et al.* over a smaller temperature interval. Fig. 4 shows the effects of variation in the pressures of the two reactants at two temperatures: we find Rate $\propto P_{CO}^{0\cdot28}$ and $\propto P_{O_2}^{0\cdot20}$ at 66° in the presence of a constant pressure of the other gas, and in confirmation of this, for the stoicheiometric (1 : 2) mixture, Rate $\propto P_T^{0\cdot48}$, where $P_T = P_{CO} + P_{O_2}$; $P_{CO} = 2P_{O_2} = \frac{2}{3}P_T$ for stoicheiometric case.

Similarly, at 48°, Rate $\propto P_{CO}^{0\cdot45}$ and $\propto P_{O_2}^{0\cdot17}$ and $\propto P_T^{0\cdot63}$. Evidently competition occurs between the two reactants and therefore since the adsorption isotherms for the mixed gases are not known the true activation energy cannot be determined. The experiments (Fig. 2) show there is a time lag between admission of gases to the bare catalyst and attainment of the steady state, of about 3 min. at 86° and 4 min. at 48°; a similar interval occurs after the injection of more of one of the reactants into a system which has reached a steady state (Fig. 3). This time lag is rather greater than that normally taken by the mass spectrometer to recover steady conditions after change of pressure behind the leak leading to the ionisation chamber, and we believe it is associated with the production of steady conditions on the catalyst surface; it is about the same as that found with pure oxygen and carbon monoxide separately at lower temperatures and pressures by Garner *et al.* (*locc. cit.*).

The desorption experiments, on pumping out after a reaction, show that the adsorbed layer during the reaction contains carbon dioxide and carbon monoxide (although no poisoning by the former was found). Oxygen must also be adsorbed, as was clearly shown by Garner, Stone, and Tiley (*loc. cit.*), but either it reacts very rapidly with adsorbed carbon monoxide or it is very strongly held and is eventually consumed by oxidation of underlying copper or in restoration of the oxidation state of a partly reduced surface. In this connection the two experiments displayed in Fig. 6, and the confirmatory one on catalyst B at room temperature, are of considerable interest: the former show that at both temperatures (48° and 155°) the carbon monoxide attacks the surface very rapidly and extracts oxygen from it, the ^{18}O content of the carbon dioxide formed rising to a maximum of 8·2% and 6·24% respectively; on catalyst B at 15° the maximum ^{18}O content was 6·77%. The experiment at 48° shows the slow fall of ^{18}O content in the product as normal oxygen from the gas phase is utilised: the carbon monoxide meanwhile shows a steady rise in ^{18}O content owing to exchange with those parts of the surface not taking part in the catalytic reaction. The curve for ^{18}O content of the latter gas includes some contribution from CO^+ fragments formed from the product, but the error from this cause is not important here. The run at 155° shows the slow rise in ^{18}O content of the carbon dioxide, the rise beginning towards the end of the oxidation reaction and continuing for some time after its completion, owing to exchange with parts of the surface not involved in the reaction: this run was too fast to yield, by manual scanning of the peaks, a record of the ^{18}O content of the carbon monoxide. The high ^{18}O content of the product at the maxima shows that the amount of isotopically normal reactive $(O)_{ads}$ present, derived from the gas phase, is small during the first stages of the reaction. If we assume the B.E.T. (N_2) surface area of the catalyst (2·21 m.^{2} g.$^{-1}$) corresponds to a surface layer of about $2{\cdot}25 \times 10^{19}$ ions of oxygen on the 4 g. of catalyst (cf. Garner, Stone, and Tiley, *loc. cit.*) and that at the maximum ^{18}O content all the ^{18}O in the product then formed has been produced by extraction of ^{18}O from the surface and not by exchange, we calculate that these figures correspond to an extraction of oxygen from 14% (48°) and 33% (155°) of the surface: the subsequent exchange of the carbon dioxide with the surface demonstrates that not all of the surface is active in the extraction reaction. After allowance for the latter exchange, the ^{18}O content of the carbon dioxide at the completion of the reaction at 155° also corresponds to extraction of oxygen from ~35% of the oxide surface. The peak ^{18}O content in the run on catalyst B at 15° corresponds to an extraction of ^{18}O from 10% of the surface.

We suggest that our observations may be interpreted in the following way:

$$CO(gas) + 2O^{2-}_{(s)} \longrightarrow (CO_3)^{2-} + (e_2/\square^-_s) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

followed by $$(CO_3)^{2-} + O_2(gas) + (e_2/\square^-_s) \longrightarrow CO_2(gas) + 2O^{2-}_{(s)} + O_{(ads)} \quad . \quad . \quad (2)$$

The reaction takes place on only a fraction of the surface sites. Reaction (2) is complex and is probably divisible into two steps:

$$O_2(gas) + (e_2/\square^-_s) \longrightarrow O^{2-}_{(s)} + O_{(ads)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a)$$

followed by

$$(CO_3)^{2-} \longrightarrow CO_2(gas) + O^{2-}_{(s)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2b)$$

Reaction (2*b*) is probably promoted by the destruction of the neighbouring F′ centre according to (2*a*). The $O_{(ads)}$ formed in reaction (2*a*) reacts as shown in (2*c*) to complete the cycle.

On the above scheme reaction (2*a*) or (2*b*) would be expected to be rate-determining. Garner, Gray, and Stone (*loc. cit.*) record that on admission of oxygen to a surface (of cuprous oxide on copper strip) saturated with carbon monoxide, *ca.* 50% of the latter could be recovered as carbon dioxide on evacuation at room temperature. On the other hand, Garner, Stone, and Tiley (*loc. cit.*), using a granular copper–cuprous oxide catalyst such as ours, found that the complex formed by adsorption of carbon dioxide on to an oxygenated surface was stable at room temperature in the presence of excess of adsorbed oxygen, but was quantitatively decomposed by excess of adsorbed carbon monoxide, giving carbon dioxide. The residual gas pressures in the system during these experiments are not recorded (although they were undoubtedly very low), but it is probable that this is an important factor; we have repeatedly found in the present work that addition of several cm. of oxygen gas to a catalyst holding adsorbed carbon monoxide causes the appearance of gaseous carbon dioxide in the reaction system (cf. Fig. 1; similar observations were made on catalyst B at 20°).

Garner, Stone, and Tiley (*loc. cit.*) suggested, for temperatures between 10° and 36°, at much lower pressures, a reaction between $O_{(ads)}$ and $CO_{(ads)}$, with the adsorption of oxygen

$$O_2(gas) \longrightarrow 2O_{(ads)} + 55 \text{ kcal. mole}^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

[which is analogous to reaction (2*a*)] as the rate-determining step; they suggested that extraction of oxygen from the surface would occur at *ca.* 70° and upwards. It is possible that in the present work the latter reaction took place at significantly lower temperatures because of the higher pressures used, but further work in this connection is desirable. The fact that our figure for E (10 ± 2 kcal. mole^{-1}) is very close to that found by Garner, Stone, and Tiley ($11{\cdot}4 \pm 2$ kcal. mole^{-1}) may indicate that both studies were concerned with the same limiting process. They noted that their value for E, if it referred to reaction (3), was not in agreement with their earlier figure of $7 \pm 1{\cdot}5$ kcal./mole for the adsorption of oxygen in the absence of other gases, but suggested that the presence of high concentrations of $(CO_3)_{ads}$ might modify the value of E. Nor for that matter does our value of E agree with that (15·5 kcal. mole^{-1}) found by us for the oxidation of copper powder (Winter, *J.*, 1954, 3342). In any case our ^{18}O results * show that lattice oxygen is largely involved in the reaction under our conditions and thus that the mechanism of the reaction on cuprous oxide is very similar to that proposed by Schwab and Drikos (*Z. phys. Chem.*, 1942, **52**, *B*, 234) for the same reaction on cupric oxide.

The experiment with a 1 : 1 mixture of normal and 30%-^{18}O for the oxidation of carbon monoxide shows that, as in the oxidation of copper (Winter, *J.*, 1954, 3342) any $O_{(ads)}$ formed is strongly adsorbed or rapidly reacts further, and does not take part in a desorption stage $2O_{(ads)} \longrightarrow O_2(gas)$ which would lead to equilibration. It is most likely that any $O_{(ads)}$ formed is labile over the surface (cf. Winter, *J.*, 1954, 1522) and reacts rapidly with a neighbouring $(CO_3)^{2-}$ complex:

$$(CO_3)^{2-} + O_{(ads)} + (e_2/\square^-_s) \longrightarrow CO_2(gas) + 2O^{2-}_{(s)} \quad . \quad . \quad . \quad (2c)$$

[This reaction, like (2) above, probably proceeds in two stages, the first being the destruction of the F′ centre.]

* Cf., in particular, the high proportion of the total reaction (~30%) which has occurred in the experiment at 155° at the maximum ^{18}O content of the carbon dioxide (Fig. 6).

The effect of pre-treating the surface with one or other of the three gases, studied at 50°, shows that neither carbon monoxide nor carbon dioxide poisons the surface appreciably, but that pre-treatment with oxygen causes a marked acceleration. The effect of oxygen is in accord with Garner's finding that $O_{(ads)}$ was very reactive; it also confirms the conclusion drawn from the reaction on a $Cu_2{}^{18}O$ surface that the concentration of $O_{(ads)}$ is low, at least during the early stages of the normal oxidation reaction with the stoicheiometric mixture. Garner, Stone, and Tiley (*loc. cit.*; cf. Dell and Stone, *Trans. Faraday Soc.*, 1954, **50**, 501) have also shown that the desorption of carbon dioxide should not be the slow stage on cuprous oxide.

(b) *Reactions on Nickel Oxide.*—Our work shows this catalyst is much less active than cuprous oxide in promoting oxygen exchange between carbon monoxide and dioxide and the surface; the exchange between oxygen gas and the surface attains a reasonable rate only above 400° (Winter, unpublished work), and thus is rather less easy to achieve than exchange between the surface and carbon dioxide, which is measurable at 250°. The oxygen exchange work gives a value of about 7×10^{19} for n_s, compared with approximately $6{\cdot}3 \times 10^{19}$ calculated from the B.E.T. (N_2) surface area. Analysing the CO-oxidation experiments on $Ni^{18}O$ in the same way as for $Cu_2{}^{18}O$ we find that the ^{18}O contents at the completion of the reaction correspond to an extraction of ^{18}O from 0·34% (49°) and 2·3% (211°) of the nickel oxide surface; all the experiments are summarised in Table 3. As noted in the Experimental section there is no appreciable exchange between any of the three gases and the surface at temperatures around 50°, but after some ten oxidation experiments in this region the majority of the ^{18}O originally present in the surface is still available for exchange at higher temperatures with oxygen and with carbon dioxide: it is clear that at the lower temperatures the extraction, and probably the whole oxidation of carbon monoxide, occurs only at a small number of very reactive fixed sites. The oxidation experiment in which a non-equilibrated $^{18}O_2$–$^{16}O_2$ mixture was used shows that, as with the reaction on cuprous oxide, no adsorption-desorption, involving dissociation of molecular oxygen, occurs during the reaction.

The oxidation kinetics may be accounted for (cf. Dell and Stone, *loc. cit.*) by assuming competition between carbon monoxide and carbon dioxide for the small number of sites left free by oxygen, which is strongly adsorbed (or for a small number of very active sites, oxygen not competing for these). [The occurrence of appreciable chemisorption of oxygen, at these temperatures and pressures, on another part of this nickel oxide preparation, has been confirmed and measured in work connected with the exchange reactions with gaseous oxygen: similar remarks apply to chromium oxide (Winter, unpublished work).] Then, if the velocity is proportional to the concentration of carbon monoxide on these sites,

$$\text{Rate} = \frac{dP_{CO_2}}{dt} = \frac{kP_{CO}}{(P_{CO} + P_{CO_2})} = \frac{k(P^i_{CO} - P_{CO_2})}{(P_{CO} + P_{CO_2})} = \frac{k(P^i_{CO} - P_{CO_2})}{P^i_{CO}} \quad . \quad (4)$$

where P^i_{CO} is the initial pressure of carbon monoxide, P_{CO} and P_{CO_2} are the pressures of the two gases at any time during the reaction, and $P^i_{CO} - P_{CO} = P_{CO_2}$.

Integration of eqn. (4) yields:

$$kt = -P^i_{CO} \log (P^i_{CO} - P_{CO_2}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Fig. 7 shows that this equation adequately represents our observations: it may be noted that the equation

$$\log (t - t_0) = \alpha g - \log a\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

used for this reaction on the same catalyst by Parravano (*J. Amer. Chem. Soc.*, 1953, **75**, 1448), derived from $dg/dt = a \exp \alpha g$, where g is the amount of conversion and α and a are constants, does not give so good a fit as eqn. (5), although it gives fair straight lines when applied to our results. Eqn. (6) has no very clear physical interpretation and in the present instance we prefer (5): the latter equation should, if our assumptions about the mechanism are correct, hold until P_{O_2} becomes so low that the surface begins to be denuded of oxygen, and in fact it appears to hold up to at least 90% conversion.

It is of interest that Parravano found eqn. (6) to hold for the first few runs on a fresh catalyst, but that after a time the activity diminished until a plot of log P_T against time gave good straight lines in the temperature region 100—180°. Over the range 180—240° on the aged catalyst the equation $-dP_T/dt = kP_T^{1.25}$ held. (Parravano removed the carbon dioxide continuously from the gas phase and followed the fall of total pressure, P_T.) We did not observe higher activity during the first few runs on any sample and we ascribe this to our practice of heating the catalyst in a high vacuum to at least 240° overnight before each run, which should remove adsorbed gases and provide a surface of standard and reproducible activity.

It should be noted that it can readily be shown that our eqn. (4) and (5) are formally the same as the log P_T–time plot used by Parravano (see his Fig. 3), after allowance for the different experimental conditions (*i.e.*, the product was removed continuously in the earlier work).

The mechanism we propose requires that the velocity constant should be little affected by moderate changes in the initial pressures of reactants, provided the ratio $P_{CO} : P_{O_2}$ is kept constant: Table 2 shows that, with the stoicheiometric mixture ($P_{CO}/P_{O_2} = 2$), a twofold change in initial pressures not change k; on the other hand a 5—6-fold increase in P_{O_2}, coupled with a 25% reduction in P_{CO}, reduces k by half. Again, the catalyst is readily poisoned by carbon dioxide, as is shown by a run at 57° in which the surface was exposed to 1·6 cm. of carbon dioxide for 10 min. and evacuated for 3 min. before addition of 3 cm. of the stoicheiometric reaction mixture; the value of k for this run was 3·2, to be compared with 5·74 for the reaction on the outgassed surface under the same conditions of temperature and pressure (cf. Table 2). Similarly a series of five successive experiments at 57° (not reported in detail here) in which the catalyst was merely evacuated at 57° for 10—15 min. between runs showed a progressive reduction in rate; mass-spectrometric examination of the gas being desorbed between experiments showed it to consist of carbon dioxide (as indeed it should, the runs being carried to completion). The oxide was restored to its original activity by outgassing overnight at 240°. The poisoning by carbon dioxide is in accord with the work of Dell and Stone (*loc. cit.*) who showed from their heat measurements that this gas might be expected to poison nickel oxide, but not cuprous oxide. The experiments in which the oxidation reaction was carried out on a $Ni^{18}O$ surface (Table 3) show that although only a very small fraction of the surface takes part in the extraction reaction, this proportion increases slowly with temperature; a plot of log x against $10^5/T$ (where x is the percentage of the surface taking part in the extraction reaction) gives $E \approx 3{\cdot}8$ kcal. mole^{-1}, while the oxidation reaction velocity constants calculated by eqn. (5) and shown in Table 2 give $E \approx 5{\cdot}5$ kcal. mole^{-1}. We find no inflexion point in the Arrhenius plot of the oxidation figures, in contrast to Parravano. This may be due to the different method of catalyst preparation (Parravano prepared his catalyst by igniting the nitrate) or (more probably) to the difference in experimental techniques, in particular to our practice of outgassing the catalyst at an elevated temperature between experiments.

Dell and Stone (*loc. cit.*), discussing Parravano's figures, suggested the reaction proceeds at lower temperatures ($E \approx 3$ kcal. mole^{-1}) *via* adsorbed species and that at higher temperatures (>160°) it proceeds by the extraction reaction with $E \approx 13$ kcal. mole^{-1}. They saw the difficulty in explaining why it occurs all at very low temperatures unless it takes place on a few very reactive sites. Dell and Stone proved that whereas an adsorption complex which they write as $(CO_3)_{ads}$ could be readily formed by the reaction of carbon monoxide or carbon dioxide with adsorbed oxygen, this complex was stable in the presence of excess of either oxygen or carbon monoxide at 20°: they were, however, able to measure the oxidation reaction quite readily at 20° and 2—8 mm.

The facts that the kinetic runs show no inconsistencies, and that each smoothly and accurately follows eqn. (5), particularly at the commencement of the reaction, coupled with the observations on $Ni^{18}O$ (see above), lead us to conclude that, as in the case of cuprous oxide, the reaction $2CO + O_2 \longrightarrow 2CO_2$ occurs, under our conditions at least, almost if not entirely by the extraction mechanism, on only a small fraction of the surface sites, the process being described by equations such as (1) and (2) above.

Since at reaction temperatures carbon monoxide alone shows no exchange on nickel

oxide, in spite of the proved presence of up to 2—3% of active sites, we conclude that in the absence of oxygen these sites are *irreversibly* covered by chemisorbed carbon monoxide which is only released as carbon dioxide by subsequent adjacent absorption of oxygen, or on considerable rise in temperature. This favours regarding reaction (2*a*) as rate-determining on this oxide. If the rate equation is written as

$$\text{Rate} = PZ \exp(-E/RT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where P is a frequency factor, and Z the number of active sites per g., Z increases on change from 49° to 211° by a factor of ~6·7, as shown by the experiments on $Ni^{16}O$; over the same temperature range the rate of oxidation increases by a factor of ~16·2. The number of reaction sites, as shown by experiments on $Ni^{18}O$, increases smoothly by an exponential function

$$Z = Z_0 \exp(-E_1/RT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

with $E_1 \approx 3{\cdot}8$ kcal. mole^{-1}; the corrected apparent E for the catalytic reaction is then, P being assumed to be constant, about 1·7 kcal. mole^{-1}.

Similar arguments, applied to the reaction on $Cu_2{}^{18}O$ at 155° and 48°, would reduce the observed value of E for the oxidation from 10 ± 2 to a corrected figure of 8 ± 2 kcal. mole^{-1}.

(c) *Reactions on Chromium Oxide.*—This oxide proved very similar to nickel oxide in its behaviour. Thus we may note: the absence of exchange with carbon monoxide and carbon dioxide until relatively high temperatures are reached; the small number of sites active in the extraction reaction during the oxidation of carbon monoxide; the very low apparent activation energy of the latter reaction; and the negligible increase in the number of active sites with increase in temperature. The oxidation also followed the same kinetic law [eqn. (5)] as on nickel oxide, but the kinetics were not so fully investigated.

The results in Tables 3 and 4 agree in showing that both the rate of the oxidation and the number of active (extraction) sites remain approximately consistent over the temperature range 44—155°, so that, in the eqns. (8) and (9) above, both E and $E_1 \approx 0$. It seems reasonable to think that the oxidation reaction follows the same course as on nickel oxide.

(d) *General.*—The present study amplifies the picture built up as a result of other work on these reactions, but although general agreement is reached on many points there are several divergences, and in particular our proposals for the mechanism of the oxidation reaction ($CO + \frac{1}{2}O_2 \longrightarrow CO_2$) on cuprous and nickel oxides at low temperatures differ fundamentally from those of Garner, Stone, *et al.* A repetition and extension of this work combining our technique with heat measurements similar to those of Garner and Stone would be valuable, since it is not certain that the catalysts used in the two laboratories are energetically similar and therefore detailed correlation of observations may not be justified at present.

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Properties of Ion-exchange Resins in Relation to Their Structure. Part VII. Cation-exchange Equilibria on Sulphonated Polystyrene Resins of Varying Degrees of Cross-linking.*

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A study has been made of the relative affinities of various pairs of univalent cations for ion-exchange resins consisting of monosulphonated polystyrenes of various degrees of cross-linking. Results are presented for all the possible combination of the four cations, H, Li, Na, and K with resins of 5, 10, 15, and 25% (nominal) divinylbenzene content. Examination of the results suggests a "natural" order of affinities: K > Na > H > Li. Inversions of affinity occurred only with systems involving hydrogen, and these inversions have been shown to be a true effect of the sulphonic groupings and not due to any "polyfunctionality" of the resins. It is concluded that the simplified form of Gregor's theory of ion-exchange affinity (*J. Amer. Chem. Soc.*, 1951, **73**, 643) does not account completely for the experimental results obtained. It is suggested that any further developments of the theory must take into account the statistical variation of cross-linking in ion-exchange resins and the relative ease with which the hydration shells of ions may lose some water molecules.

Reichenberg, Pepper, and McCauley (*J.*, 1951, 493) investigated the sodium–hydrogen equilibria on a number of monosulphonated styrene–divinylbenzene copolymers with varying degrees of cross-linking. This work has now been extended to elucidate some of the fundamental factors governing ion-exchange equilibria by studying various pairs of cations. Since it was desired to eliminate as far as possible such complicating factors as ion-pair and complex-ion formation, the study was confined to the hydrogen ion and ions of the alkali-metals. (However there are grounds for believing that in some respects the hydrogen ion behaves anomalously.) The ion-exchange equilibria of all the possible pairs of ions arising from the series hydrogen, lithium, sodium, and potassium have been studied on sulphonated cross-linked polystyrene resins of 5, 10, 15, and 25% (nominal) divinylbenzene contents. All measurements were made at 25° and from solutions of virtually infinite dilution (with one exception).

Experimental

Determination of Relative Affinity Coefficients.—The method used was essentially the same as that described previously (Reichenberg, Pepper, and McCauley, *loc. cit.*), but whereas the previous work was carried out at 22—25°, in the present study the conditioning process was carried out in an air-thermostat at 25·0° ± 0·1°. The conditioning solution (initially in a vessel outside the thermostat) flowed to the column of resin through coils of glass tubing which even with the highest flow rate used and the highest temperature difference between the inside and the outside of the thermostat ensured that its temperature was within 0·1° of that required.

In the previous work, and also for the sodium–hydrogen equilibria reported in the present work, all conditioning solutions had a concentration of 0·1125N, and after conditioning, the excess of liquid was drained off, a correction being applied for the electrolyte in the small amount of liquid left. For all other equilibria reported in the present paper, the resin was first conditioned with a 0·1N conditioning solution, then with a further amount diluted to 0·05N, then 0·02N, then 0·01N, and finally the resin was washed with water. The amounts of the diluted conditioning solutions and the flow rates used were such as to try to ensure that the ion-exchange equilibrium, if it was dependent on the total concentration, would not be "frozen" at a position corresponding to a concentration greater than 0·01N. It has been assumed that variation of solution concentration below 0·01N has no further effect on the resin composition. As in the earlier work, completeness of conditioning and the absence of hysteresis effects have been demonstrated by approaching the equilibrium from both directions.

* Part VI, *J.*, 1953, 4097.

In systems involving the hydrogen ion, this ion alone was determined, the amount of the other ion on the resin being obtained by difference from the total ion-exchange capacity of the resin sample (about 2·5 m.-equivs.). With other pairs of ions, both ions were eluted from the resin with 2N-hydrochloric acid, and the total volume made up to 50 ml. with 2N-acid. The amounts of the two ions in the eluate were then determined with a Beckman DU Flame Spectrophotometer, made-up standard solutions containing hydrochloric acid and the chlorides of the two ions being used. The composition of these standard solutions was adjusted so that (*a*) the total chloride ion concentration was 2N, (*b*) the sum of the concentrations of the two cations was the same as in the made-up eluate solution; (*a*) and (*b*) being kept fixed, standards were made up containing various amounts of the two cations. This enabled the exact amounts of the two ions in the eluate solution to be determined separately. It was found in all cases that their sum agreed within experimental error (±2%) with the known total exchange capacity of the sample of resin used.

In the first part of this work, the analyses for the sodium–potassium equilibria were carried out by determining the sodium gravimetrically by means of zinc uranyl acetate and obtaining the potassium concentration by difference. These results were later checked by use of the flame photometer.

Materials.—Resins. The resins used were similar to, but not identical with, those used in the previous work. A brief account of this difference has been given in another paper (Pepper, Reichenberg, and Hale, *J.*, 1952, 3129). The resins of the present work were prepared from the commercial (approximately 50%) divinylbenzene. Differences between these resins and corresponding resins of the other series are small. The properties of the resins used are given in Table 1.

TABLE 1.

Nominal divinylbenzene content (%)	Particle diameter (swollen in water) (μ)	Specific capacity (m-equivs. per g. dry H-form resin) (1) Found	(2) Calc.[a]	(3) Calc.[b]	Weight swelling (g. of H_2O absorbed per amount of resin equivalent to 1 g. dry H-form resin) H-form	Li-form	Na-form	K-form
5½	200—250	5·40	5·38	5·37	1·49	1·48	1·26	1·11
10	150—250	5·30	5·30	5·31	0·84	—	0·73	0·62
15	130—220	5·24	5·25	5·25	0·60	—	0·53	0·45
25	100—250	*	4·83	5·11	0·38	0·36	—	—

[a] Calculated from the sulphur content. [b] Calculated assuming monosulphonation of each benzene ring.

* This resin was polyfunctional and its specific capacity increased with increasing pH. In 0·1N-NaCl solution, the specific capacity of 4·83 (calculated from the sulphur content) was realised at pH 3·8, but at pH 12 the capacity was nearly 5·1.

The weight swellings were determined with the centrifuge (Pepper, Reichenberg, and Hale, *loc. cit.*). While absolute values of the weight swellings cannot be relied upon to better than ±0·01, the difference in weight swelling of two different cationic forms of the same resin can be determined to within ±0·003.

Conditioning solutions. All the conditioning solutions were made from appropriate mixtures of 2N-HCl, -LiCl, -NaCl, and -KCl. The last two solutions were made up by weighing out appropriate quantities of " AnalaR " materials which had been dried overnight at 110°. The lithium chloride solution was made by precipitating the carbonate, washing and drying it, and then decomposing a known weight with concentrated hydrochloric acid, followed by evaporating to dryness twice and redissolving. The concentrations of the chloride solutions were checked by using standard ion-exchange procedures described by Samuelson (" Ion Exchangers in Analytical Chemistry," John Wiley and Sons, Inc., New York; Almquist and Wiksell, Stockholm, 1953, Chapter VIII). For use, known volumes of two of the standard 2N-solutions were accurately made up together and diluted to approximately 0·1N total cation concentration.

DISCUSSION

The relative affinity coefficient K_A^B of two ions A and B (of the same valency) for a resin is defined as

$$K_A^B = \frac{[B_R]}{[A_R]} \cdot \frac{[A_S]}{[B_S]} \cdot \frac{(f_A)_S}{(f_B)_S} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $[A_R]$ and $[B_R]$ are the amounts of A and B on the resin, $[A_S]$ and $[B_S]$ are the concentrations in solution, and $(f_A)_S$ and $(f_B)_S$ are the activity coefficients of the ions in solution. [$(f_A)_S$ and $(f_B)_S$ cannot of course be evaluated separately though their ratio is determinate.] If the final equilibration is done in solutions of virtually infinite dilution, the activity coefficient ratio in solution may be taken as unity. In 0·1N-solutions, however, this ratio usually differs from unity by a few percent.

For convenience, our results are given as plots of log K_A^B against $(X_B)_R$, where $(X_B)_R$ is the equivalent fraction of B on the resin (Figs. 1—6).

It will be observed that the present results on the Na–H system agree quite well with those previously reported (Reichenberg, Pepper, and McCauley, *loc. cit.*). Such differences as occur increase with increased cross-linking and are undoubtedly due to differences in the preparation of the resins (see above). Where comparison is possible, the present results agree roughly with those of Bonner and his co-workers (Bonner and Rhett, *J. Phys. Chem.*, 1953, **57**, 254; Bonner and Payne, *ibid.*, 1954, **58**, 183; Bonner, *ibid.*, p. 318), but there are more marked differences in the case of the Li–H system. Gregor and Bregman's results (*J. Colloid Sci.*, 1951, **6**, 323) do not agree well with either those of Bonner or our own. These differences are probably mainly due to differences in the resins used, though differences of experimental technique in the determination of relative affinities may also play some part.

In general, for a given pair of ions and a given resin, the relative affinity coefficient varies with the cationic composition of the resin. In nearly all cases, log K_A^B decreases with increasing $(X_B)_R$, *i.e.*, the affinity of the resin for a given ion decreases with increase in the amount of that ion on the resin. Some apparent exceptions are of interest: (1) In the sodium–lithium system, minima are found with the 5% and 10% divinylbenzene resins. These are very shallow and may be within experimental error. (2) In the sodium–hydrogen system, a maximum is found with the 5% divinylbenzene resin. The sodium–hydrogen equilibria were the only ones examined in 0·1N-solution; all the others were studied in solutions of virtually infinite dilution.

These considerations suggest that, in the alkali-metal series, all equilibria in solutions of infinite dilution may conform to the pattern of decreasing K_A^B with increasing $(X_B)_R$.

Both the relative affinity differences themselves and their variation with the cationic composition of the resin increase markedly with increase in the degree of cross-linking. Separate experiments have shown that a resin of only ½% divinylbenzene has K values which are always unity.

It will be observed that the six systems may be divided into two types: (*a*) Those in which an inversion of log K can occur, *i.e.*, log K changes sign with variation of cationic composition. This occurs only in the systems involving the hydrogen ion, Li–H, Na–H, and K–H (Figs. 1, 2, and 3), and only with resins of high cross-linking (15 and 25% divinylbenzene). (*b*) Those in which no inversion occurs. This group comprises the systems Li–Na, Li–K, and K–Na (Figs. 4, 5, and 6).

It was suggested earlier (Reichenberg, Pepper, and McCauley, *loc. cit.*) that inversions might be due to "polyfunctionality" in the resins of high cross-linking rather than a "true" effect of the sulphonic acid groups. This explanation is, however, disproved by the results on the lithium–hydrogen system, for on this basis in Fig.1, the preference for hydrogen should occur at lower values of $(X_{Li})_R$ for the 25% divinylbenzene resin than for the 15% resin, but the reverse is found. This can only be explained by supposing either that the carboxyl groups have an exceptionally high affinity for the lithium ions, higher even than for hydrogen ions, or that the inversion is a true effect of the sulphonic acid groups. The latter explanation is far more probable, and it is clear that the inversion phenomenon is bound up with the unique character of the hydrogen ion.

Among the systems of type (*b*) log K_A^B keeps the same sign for a given pair of ions not only with varying cationic composition but also with varying cross-linking. Thus, log K_{Li}^{Na}, log K_{Li}^{K}, and log K_{Na}^{K} are always positive, so that we may, in a loose sense, write down a "natural" order of affinities K > Na > Li. In Figs. 4—6, A and B have been so chosen as to make log K_A^B positive. With this convention, log K_A^B increases continually with increasing cross-linking at low values of $(X_B)_R$. This is not so at high values of

FIG. 1. *Hydrogen–lithium exchange.*

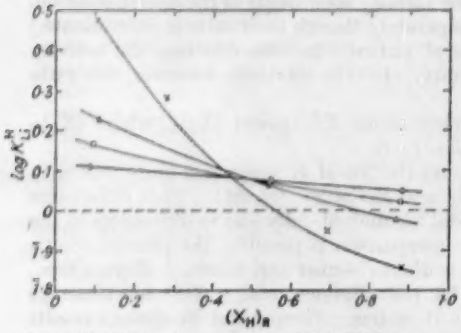


FIG. 2. *Sodium–hydrogen exchange.*

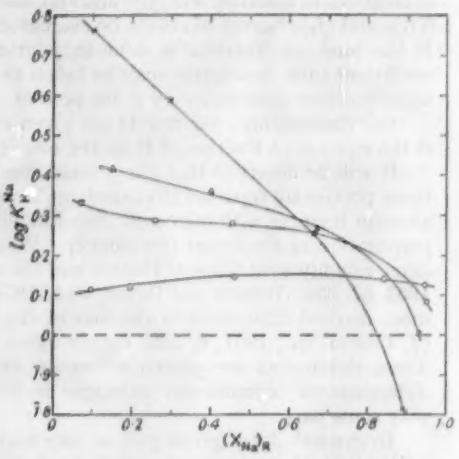


FIG. 3. *Potassium–hydrogen exchange.*

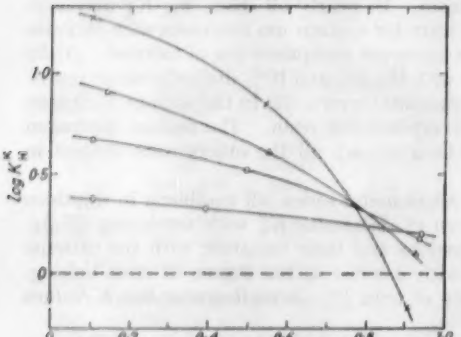


FIG. 4. *Sodium–lithium exchange.*

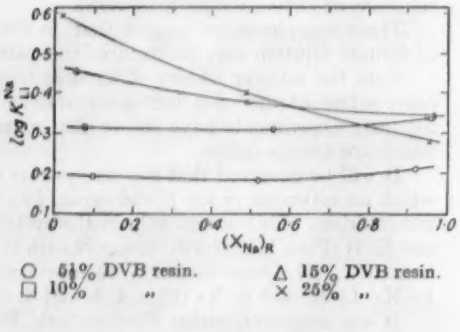


FIG. 5. *Potassium–lithium exchange.*

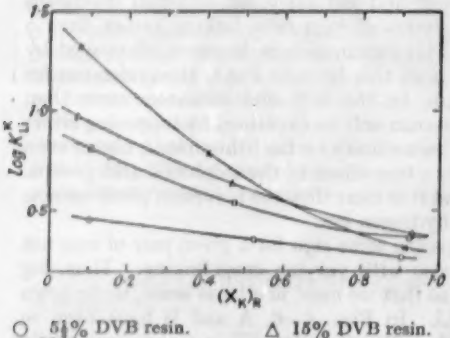
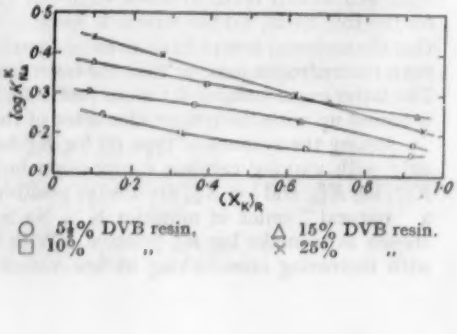


FIG. 6. *Potassium–sodium exchange.*



all purely theoretical attempts to account quantitatively for the activity coefficients of

$(X_B)_R$ since some of the curves cross. (This irregularity appears to be primarily centred in the 25% divinylbenzene resin whose curve in each case crosses at least one of the other curves.) Thus there is a regular effect of cross-linking on the relative affinity provided that the resin is predominantly in the form of the ion of lower " natural " affinity.

For systems of type (*a*) we cannot apply the simple criterion of the sign of $\log K_A^B$ to find which ion has the higher " natural " affinity for the resin. However, three regularities may be noted: (1) At low and intermediate degrees of cross-linking, no inversion occurs and $\log K$ keeps the same sign with varying cross-linking. On the basis of the sign of $\log K_A^B$ within this restricted range of cross-linking, we obtain the order of affinities K > Na > H > Li. (2) If we assume (in accordance with this order) that lithium has a lower " natural " affinity than hydrogen, then to conform to our previous convention $\log K_{Li}^{H}$ should be plotted against $(X_H)_R$ (Fig. 1) rather than $\log K_H^{Li}$ against $(X_{Li})_R$. It is then found (Figs. 1, 2, and 3) that at low values of $(X_B)_R$, $\log K_A^B$ increases continually with increase of cross-linking *over the whole range of cross-linking*. (3) Provided this convention be adopted, we find that in all cases where inversion occurs, it does so at a lower value of $(X_B)_R$ for the 25% divinybenzene resin than for the 15% one, B being the ion of higher " natural " affinity.

Thus, despite the complication of inversions, there appears to be a " natural " order of affinities K > Na > H > Li.

The order K > Na > Li is also the order of decreasing ionic mobilities and of numerous other physicochemical properties, all of which are agreed to depend on the size of the *hydrated* cation. These results confirm the view (Boyd, Schubert, and Adamson, *J. Amer. Chem. Soc.*, 1947, **69**, 2818) that ion-exchange affinity (at least with these simple cations) is determined primarily by the size of the hydrated ion, ions of small hydrated volume being preferred to large ions. It is also accepted that the hydrated hydrogen ion is larger than that of sodium. However, some doubt attaches to the implication that the hydrated lithium ion is larger than that of hydrogen. This point is discussed later.

Theoretical discussion

Gregor (*J. Amer. Chem. Soc.*, 1948, **70**, 1293; 1951, **73**, 643) represents the behaviour of ion-exchange resins in terms of a model involving an outward swelling pressure due to the osmotic activity of the ion-exchange groups and an inward counter-pressure due to the elastic forces of the cross-linked network. At equilibrium the two pressures are balanced. From this model, Gregor derived the general expression

$$RT \ln K_A^B = RT \ln \left(\frac{f_A}{f_B}\right)_R + \pi (V_A - V_B) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where K_A^B is as previously defined and π is the swelling pressure in the resin. π may be obtained unambiguously from the swelling isotherm of the resin if this is compared with that for a resin of low cross-linking or correlated with the osmotic properties of solutions of the corresponding linear polyelectrolyte. V_A and V_B are the volumes of the ions in the resin and $(f_A/f_B)_R$ is the ratio of the activity coefficients of these ions in a hypothetical resin identical in composition with the real one but not acted upon by the elastic counter-pressure. Gregor's general formulation has been widely adopted. The actual magnitudes of V_A, V_B, and $(f_A/f_B)_R$, and hence the relative magnitudes of the two terms on the right-hand side of equation (2), are affected markedly by the convention adopted in defining the components A and B. If A and B are the unhydrated ions, V_A and V_B will be very small and $(f_A/f_B)_R$ will differ greatly from unity. Hence the first term on the right-hand side of equation (2) will greatly outweigh the second. To proceed with this treatment it is necessary to develop a theoretical or semi-theoretical treatment which will enable values of $(f_A/f_B)_R$ to be predicted. This presents considerable difficulties though theories of this type have been developed and are discussed below (Glueckauf, *Proc. Roy. Soc.*, 1952, *A*, **214**, 207; Davies and Yeoman, *Trans. Faraday Soc.*, 1953, **49**, 968, 975).

The difficulty of predicting values of $(f_A/f_B)_R$ theoretically lies, of course, in the fact that

exactly the opposite of that found when the resins are predominantly in the form of lower

isoelectronic nitrogen atom: the former having a bond whose b_L is nearly equal to its b_T or b_V (cf. *J.*, 1954, 1577), the latter carrying a lone pair whose contributions to b_2 and b_3 should presumably be the same. For many physical properties, of course, this replacement

TABLE 6. *Values of* b_i^{base} *minus* $b_i^{hydrocarbon}$.

	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$	$10^{23}\Delta b_1$	$10^{23}\Delta b_2$	$10^{23}\Delta b_3$
C_5H_5N	1·06	1·13	0·553	−0·05	+0·01$_5$	−0·18
C_6H_6 *	1·11$_4$	1·11$_4$	0·733			
C_9H_7N	1·65	2·24	0·795	−0·11	+0·09	−0·23$_5$
$C_{10}H_8$ †	1·76	2·15	1·03			
iso-C_9H_7N	2·00	1·91	0·752	−0·05	+0·05	−0·28
$C_{10}H_8$ ‡	2·05	1·86	1·03			

* From *J.*, 1954, 1577.
† From *J.*, 1955, 1641, where b_1 of naphthalene corresponds to the b_3 direction of quinoline.
‡ The b's shown are calculated from those of naphthalene, via $b_1\beta = b_1^{C_{10}H_8}\cos^2 30° + b_2^{C_{10}H_8}\sin^2 30°$, etc.

causes little alteration (*e.g.*, for spectra, see Bowen, *Ann. Reports*, 1943, **40**, 25). Perhaps the contributions of structures such as (d) shown by Coulson ("Valence," Oxford, 1952, p. 241) are not negligible.

Molar Kerr Constants of Pure Pyridine and Quinoline.—The B's for these two substances may be deduced from the measurements, relatively to carbon disulphide, reported by Leiser (*Abhand. Deut. Bunsen-gesellschaft*, No. 4, Halle a.S., 1910) and Lippmann (*Z. Elektrochem.*, 1911, **17**, 15), *viz.*, 6·32 and 4·66. The value of $B_{20}^{CS_2}$ being taken as $3{\cdot}226 \times 10^{-7}$, the B's of pyridine and quinoline are $20{\cdot}4 \times 10^{-7}$ and $15{\cdot}0 \times 10^{-7}$ respectively. The molar Kerr constant of the pure liquid then follows as ${}_mK_{liq.} = 6B\lambda nM/(n^2+2)^2(\varepsilon+2)^2d$; Table 7 contains the necessary data. While ${}_mK_{liq.}$ is

TABLE 7. *Empirical correction of* ${}_mK_{liq.}$.

	10^7B_1	d	n	ε	$10^{13}{}_mK_1$	$(10^{13}{}_mK)\varepsilon/n^3$
Pyridine	20·4	0·978	1·5074	12·01	24·5	130
Quinoline	15·0	1·090	1·625	8·704	43·6	144

considerably smaller than ${}_\infty({}_mK_2)$—listed in Table 1—application of the empirical correction suggested by Le Fèvre and Le Fèvre (*J.*, 1953, 4041) produces figures which approach the orders of those now obtained at infinite dilution.

EXPERIMENTAL

Materials, Apparatus, and Methods.—The solutes were originally pure commercial samples but were dried and refractionated immediately before preparation of solutions. The carbon tetrachloride was part of the bulk described in *J.*, 1954, 1577. The apparatus, details of procedure, and calculation remain as noted in *J.*, 1953, 4041, wherein the symbols found in the following Tables are defined. Observations are recorded in Table 8, and computations of ${}_\infty({}_mK_2)$ summarised in Table 9; λ has been taken as 5893 Å.

TABLE 8. *Kerr constants and refractive indexes of solutions in carbon tetrachloride at* 25°.

	Pyridine					
10^3w_2	206	628	801	1512	1538	4043
$10^7\Delta B$	0·025	0·128	0·160	0·275	0·293	0·831
n_D	—	—	—	1·4590	1·4591	1·4616

whence $10^7\Delta B = 18{\cdot}1w_2 + 60w_2^2$ and mean $\gamma n_1 = 0{\cdot}102$.

	Quinoline					iso*Quinoline*				
10^4w_2	1174	2209	3708	5157	5641	76	530	965	2126	3298
$10^7\Delta B$	0·113	0·284	0·543	0·759	0·884	0·026	0·217	0·382	0·957	1·510
n_D	—	—	1·4661	1·4695	1·4706	—	—	—	1·4625	1·4652
	whence $10^7\Delta B = 11{\cdot}0w_2 + 81w_2^2$ and mean $\gamma n_1 = 0{\cdot}232$.					whence $10^7\Delta B = 40{\cdot}3w_2 + 173w_2^2$ and mean $\gamma n_1 = 0{\cdot}234$.				

The temperature used throughout was 25°, for which the appropriate solvent constants are: $10^7B = 0{\cdot}070$; $n_D = 1{\cdot}4575$; $d_4^{25} = 1{\cdot}5845$; $\varepsilon = 2{\cdot}2270$; $H = 2{\cdot}060$; $J = 0{\cdot}4731$; $10^{13}{}_sK_1 = 0{\cdot}0749$.

It will be noted that between quinoline and *iso*quinoline, on one hand, and α- and β-naphthyl derivatives, on the other, the relative magnitudes of the molar Kerr constants at infinite dilution

TABLE 9. *Calculation of molar Kerr constants at infinite dilution.*

Solute	α_1 *	β *	γ	δ	$\infty(_mK_2) \times 10^{12}$
Pyridine	13·88	−0·582	0·070	258	150
Quinoline	8·25	−0·443	0·159	157	149
*iso*Quinoline	11·0	−0·424	0·161	576	572

* From unpublished measurements by Freeman, Le Fèvre, Rao, and Tardif.

show similar trends: $\infty(_mK_2)$ of *iso*quinoline is roughly four times that of quinoline, while β-$C_{10}H_7X$—when X = F, Cl, Br, or I—usually has a molar Kerr constant 2—3 times that of its α-isomer (cf. *J.*, 1955, 1641).

We thank the Royal Society, and Imperial Chemical Industries, Australia and New Zealand, Ltd., for grants with which our apparatus has been purchased.

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*Some Products formed from Phenolic Inhibitors during the Autoxidation of Cumene. Part II.**

By (MISS) M. E. HEY and WILLIAM A. WATERS.

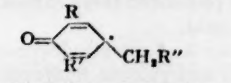
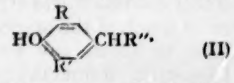
[Reprint Order No. 6214.]

Representative 2 : 4 : 6-trialkylphenols have been oxidised with air in cumene solution. The only products which could be isolated are those derived from substituted 4-hydroxybenzyl radicals (II), *e.g.*, 4-hydroxyaryl ketones and 4 : 4′-dihydroxydibenzyl derivatives, and not products derived from aryloxy-radicals (I).

IN Part I,* Moore and Waters reported that, whereas autoxidising cumene brought about conversion of *p*-cresol, 2 : 4-xylen-1-ol, and 2 : 6-xylen-1-ol into dihydroxydiphenyl derivatives, mesitol, 2-*tert.*-butyl-4 : 6-dimethylphenol and 2 : 6-di-*tert.*-butyl-4-methylphenol gave dihydroxydibenzyl derivatives (III; R, R′ = Me or Bu^t, R″ = H). Attention was drawn to this evidence of autoxidative chain-breaking by 2 : 4 : 6-trialkylphenols, owing to formation of 4-hydroxybenzyl radicals (II) (reaction 2) instead of the expected mesomeric aryloxy-radicals (I) (reaction 1):

(1) $Ph{\cdot}CMe_2{\cdot} + HO{\cdot}Ar \longrightarrow Ph{\cdot}CHMe_2 + {\cdot}O{\cdot}Ar$

(2) $Ph{\cdot}CMe_2{\cdot} + HO{\cdot}C_6H_2R_2{\cdot}CH_2{\cdot} \longrightarrow Ph{\cdot}CHMe_2 + HO{\cdot}C_6H_2R_2{\cdot}CH_2{\cdot}$

(I)  (II) 

Since 4-*n*-alkyl-2 : 6-di-*tert.*-butylphenols are particularly good inhibitors of the autoxidation of hydrocarbon oils (Wasson and Smith, *Ind. Eng. Chem.*, 1953, **45**, 197) it was of interest to examine the extent to which such phenols gave products derived from radical (II).

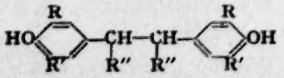
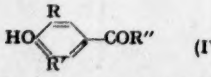
To facilitate somewhat the isolation of products, and to allow direct comparison with Bickel and Kooyman's observations (*J.*, 1953, 3211) on the oxidation of trialkylphenols with cumene hydroperoxide, cobalt phthalate has been substituted for ferric stearate as the metallic-salt catalyst and the autoxidation, effected by air at 80—100°, has been initiated by a little cumene hydroperoxide. As shown in the annexed Table, 4-ethyl-2 : 6-dimethylphenol resembled mesitol in giving a dibenzyl derivative (III; R = R′ = R″ = Me)

* This investigation continues that of *J.*, 1954, 243, which is considered as Part I.

whilst with the other compounds examined the *para*-side-chains were oxidised rather more completely to give the hydroxy-ketones (IV), accompanied in one case by a little of the

Phenol oxidised	Products isolated
4-Ethyl-6 : 6-dimethylphenol	4 : 4′-Dihydroxy-α : α′ : 3 : 5 : 3′ : 5′-hexamethyldibenzyl
2 : 6-Di-*tert.*-butyl-4-ethylphenol	3 : 5-Di-*tert.*-butyl-4-hydroxyacetophenone 2 : 6-Di-*tert.*-butyl-4-2′-hydroxyethylphenol (trace)
2-*tert.*-Butyl-4-ethyl-6-methylphenol	3-*tert.*-Butyl-4-hydroxy-5-methylacetophenone
2 : 6-Di-*tert.*-butyl-4-propylphenol	3 : 5-Di-*tert.*-butyl-4-hydroxypropiophenone
4-Benzyl-2 : 6-dimethylphenol	4-Hydroxy-3 : 5-dimethylbenzophenone

corresponding methanol. Oxidation of the phenols was never complete (recoveries 20—40%) and the yields of purified oxidation products were only about 2%, but apart from dark polymeric material no appreciable quantities of other products could be isolated from autoxidised mixtures so that a good percentage of each phenol seemed to have been destroyed completely.

(III)  (IV) 

For 2 : 4 : 6-trialkylphenols, substituted in the 4-position by methyl or *tert.*-butyl, there is considerable experimental evidence to indicate that some free-radical-producing agents, such as benzoyl peroxide (Cosgrove and Waters, *J.*, 1951, 388), acetyl peroxide (Wessely and Schinzel, *Monatsh.*, 1953, **84**, 425), lead tetra-acetate (*idem*, *ibid.*), and alkyl hydroperoxides (Campbell and Coppinger, *J. Amer. Chem. Soc.*, 1952, **74**, 1469; Bickel and Kooyman, *loc. cit.*) and one-electron-abstracting reagents such as alkaline ferricyanide (Cook and Woodworth, *J. Amer. Chem. Soc.*, 1953, **75**, 6242; Müller and Ley, *Chem. Ber.*, 1954, **87**, 922) can yield aryloxy-radicals with chemical reactivity indicative of structure (I). However, with 2 : 6-dialkyl-4-methylphenols only a very slight change in reaction conditions is needed to produce instead 4 : 4′-dihydroxydibenzyl derivatives (III) or stilbenequinones, indicative of the formation and subsequent dimerisation of isomeric but not mesomeric radicals (II). All our present work indicates that autoxidation of the 2 : 4 : 6-trialkylphenols occurs by way of substituted benzyl radicals (II). It has been suggested (Wessely and Schinzel, *loc. cit.*) that derivatives of (II) are formed from those of (I) by molecular rearrangement, but the occurrence of such rearrangements has been established only under conditions of heterolysis: to explain the formation of dimers (III) in this way one would have to suppose that the change (I) ⟶ (II) is also a favourable homolytic hydrogen transfer.

Now it is significant that the products which have been isolated from the 2 : 4 : 6-trialkylphenols listed above are structurally similar to those which can be obtained by autoxidation of the corresponding 1 : 3 : 5-trialkylbenzenes. In view of the small yields of isolated products it is possible therefore that the oxidations established by this work are side reactions (reaction 2) in which the strictly hindered phenolic group is not concerned, and that the concurrent oxidation, *via* (I), has proceeded more extensively, leading to the complete breakdown of much of the original phenol.

It was not possible to isolate any 4-hydroxy-3 : 5-dimethylbenzophenone after direct reaction between 4-benzyl-2 : 6-dimethylphenol and cumene hydroperoxide. This affords some support for the view that the side-chain oxidation is effected, as shown (reaction 2), by the cumyl radical, $Ph\cdot CMe_2\cdot$, and not by the cumylperoxy, $Ph\cdot CMe_2\cdot O\cdot O\cdot$, or cumyloxy, $Ph\cdot CMe_2\cdot O\cdot$, radicals which have been shown to yield derivatives of radical (I) (Bickel and Kooyman, *loc. cit.*).

Experimental

2 : 6-Di-*tert.*-butyl-4-ethyl- and -4-propyl-phenol were prepared by Fries rearrangement of phenyl acetate and phenyl propionate, reduction of the resulting *p*-ketones by the Huang-Minlon method, and then exhaustive butylation with *iso*butene (Stevens, *Ind. Eng. Chem.*, 1943, **35**, 655). 4-Benzyl- and 4-ethyl-2 : 6-dimethylphenol were prepared in a similar way from 2 : 6-xylen-1-ol; 2-*tert.*-butyl-4-ethyl-6-methylphenol had been prepared similarly in the laboratory of the Coal Tar Research Association.

The oxidations were carried out by blowing air at 80—100° into the purified phenol (10 g.), dissolved in cumene (400 ml.) containing cobalt phthalate (0·5 g.), cumene hydroperoxide (2 ml.) being added to initiate reaction. After the requisite time most of the cumene was distilled off; the remainder, in ether, was washed with dilute acid, then distilled in steam, and the involatile residue was dried and chromatographed through acid-washed alumina. Unchanged phenols were eluted with light petroleum–benzene, and the crystallisable products with benzene–ether or benzene–chloroform. Dark tar from which no pure products could be obtained remained on the column. The ketonic products all showed the characteristic Aryl-CO absorption band at 6·0—6·1 μ, and the methyl ketones gave positive iodoform reactions.

In 100 hr. 2-*tert.*-butyl-4-ethyl-6-methylphenol gave 0·4 g. of 3-tert.-*butyl-4-hydroxy-5-methylacetophenone*, m. p. 126° (from aqueous alcohol) (Found: C, 75·7; H, 8·5. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%).

In 72 hr. 2 : 6-di-*tert.*-butyl-4-ethylphenol (m. p. 44°) gave 0·21 g. of 3 : 5-*di*-tert.-*butyl-4-hydroxyacetophenone*, m. p. 148° [from light petroleum (b. p. 40—60°)] (Found: C, 77·5; H, 9·6. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·75%), and 0·1 g. of 2 : 6-*di*-tert.-*butyl-4-2'-hydroxyethylphenol*, m. p. 103° [from light petroleum (b. p. 40—60°)] [Found: C, 76·8; H, 10·5%; *M* (Rast), 223. $C_{16}H_{26}O_2$ requires C, 76·8; H, 10·4%; *M*, 250]. The latter product had no ketonic absorption bands, but had doubled hydroxyl bands at 2·93 and 3·18 μ.

In 100 hr. 2 : 6-*di*-tert.-*butyl-4-propylphenol*, b. p. 155°/15 mm. (Found: C, 82·1; H, 11·6. $C_{17}H_{28}O_2$ requires C, 82·3; H, 11·3%), gave 0·4 g. of 3 : 5-*di*-tert.-*butyl-4-hydroxypropiophenone*, m. p. 136° (from light petroleum) (Found: C, 77·6; H, 9·9. $C_{17}H_{26}O_3$ requires C, 77·8; H, 10·0%). After 48 hr. 4-ethyl-2 : 6-dimethylphenol, m. p. 37°, gave 0·47 g. of 4 : 4'-*dihydroxy*-α : α' : 3 : 5 : 3' : 5'-*hexamethyldibenzyl* which crystallised from benzene–ether in pale orange needles, m. p. 234° [Found: C, 80·4; H, 8·95%; *M* (Rast), 237. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·7%; *M*, 298]. The absorption spectrum, which showed no ketonic bands, very closely resembled that of 4 : 4'-dihydroxy-3 : 5 : 3' : 5'-tetramethyldibenzyl (Moore and Waters, *loc. cit.*). No crystalline product was obtained when oxidation was prolonged to 100 hr.

In 100 hr. 4-benzyl-2 : 6-dimethylphenol, m. p. 67·5°, b. p. 195—200°/20 mm., gave 0·7 g. of 4-hydroxy-3 : 5-dimethylbenzophenone, m. p. and mixed m. p. 143° (Found: C, 79·7; H, 6·2. Calc. for $C_{15}H_{14}O_2$: C, 79·7; H, 6·2%); 5 g. of the unchanged phenol were recovered. No similar product was obtained when the 4-benzyl-2 : 6-dimethylphenol was boiled for 12 hr. in benzene with 4 mol. of cumene hydroperoxide and a trace of cobalt salt.

This work was carried out on behalf of the D.S.I.R. Road Tar Research Committee. We thank the Director of the Research Laboratory of the Coal Tar Research Association (Gomersal) for a gift of 2-*tert.*-butyl-4-ethyl-6-methylphenol.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, March 9th,* 1955.]

Xanthones and Thioxanthones. Part VI. The Preparation and Properties of 9-Thia-3-aza-anthrone.*

By S. KRUGER and FREDERICK G. MANN.

[Reprint Order No. 6223.]

The preparation of 9-thia-3-aza-anthrone (which completes the series of the four isomeric 9-thia-aza-anthrones) and of certain derivatives is described. 9-Oxa-3-aza-anthrone has been synthesised, but only in low yield. The 9-thia-compound and its methochloride are ineffective as schistosomicides.

THE synthesis and properties of 9-oxa-1-aza-, 9-thia-1-aza-, 9-thia-2-aza-, and 9-thia-4-aza-anthrone have been described in Parts III—V.* We have now prepared 9-thia-3-aza-anthrone (V), which is the remaining isomer in this thia-series.

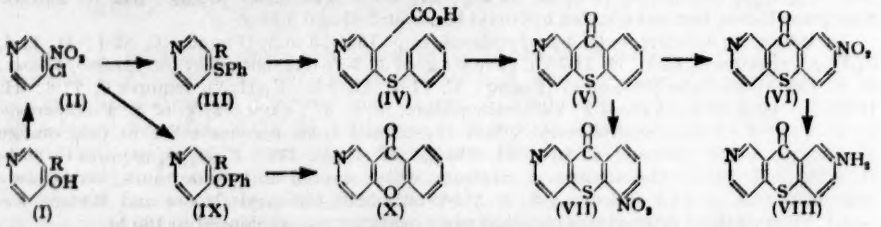
The general method adopted for the synthesis of the above 1-aza-, 2-aza- and 4-aza-anthrones consisted essentially in the introduction first of the carboxylic acid group and then of the SPh group into the appropriate positions in the pyridine nucleus: the acid was then converted into the acid chloride, which was condensed with the phenyl residue to give

* Parts III—V, *J.*, 1951, 761; 1952, 2057; 1954, 3905.

the desired 9-thia-aza-anthrone. Syntheses on these lines, introducing first either the carboxy- or the cyano-group into the pyridine ring, uniformly failed in the 3-aza-series.

Consequently, 4-hydroxypyridine was nitrated, to give 4-hydroxy-3-nitropyridine (I; R = NO_2), which in turn gave 4-chloro-3-nitropyridine (II). A cold equimolecular mixture of this with thiophenol, when carefully warmed to *ca.* 20°, underwent a sudden and violent reaction with complete solidification but no loss of hydrogen chloride. This product melted at *ca.* 190° with vigorous evolution of hydrogen chloride, forming 3-nitro-4-pyridyl phenyl sulphide (III; R = NO_2) which on reduction gave the 3-amino-sulphide (III; R = NH_2) and then, by diazotisation and treatment with potassium iodide, 3-iodo-4-pyridyl phenyl sulphide (III; R = I).

It is noteworthy that 3-cyano-4-pyridyl phenyl sulphide (III; R = CN) was obtained by treating the diazotised amino-compound with potassium cuprocyanide and by heating the iodo-compound with an excess of dry cuprous cyanide: in both cases the yield was very low, and all attempts to hydrolyse the nitrile to the required 3-carboxy-4-pyridyl phenyl sulphide (IV) caused extensive decomposition.



The preparation of a Grignard reagent from the 3-iodo-sulphide (III; R = I) could not be satisfactorily achieved, for the sulphide is insoluble in diethyl ether, and in di-*n*-amyl ether solution it rapidly coats the magnesium with a white insoluble film which prevents further reaction. Gilman and Spatz (*J. Amer. Chem. Soc.*, 1940, **62**, 446) have shown that halogenopyridines can be converted by *n*-butyl-lithium into lithiopyridines if a low temperature and a short reaction time are employed: otherwise butylation of the pyridine ring may occur. For example, they converted 3-bromoquinoline into the lithio-derivative at −35° using a metalation time of 15 minutes: Murray, Foreman, and Langham (*ibid.*, 1948, **70**, 1037), using 3-bromopyridine, reduced the metalation time to 5 minutes.

We have briefly investigated the yield of the acid (IV) obtained when the iodo-sulphide (III; R = I) and *n*-butyl-lithium are allowed to react in toluene at various temperatures and for various times, the product being then treated with an excess of solid carbon dioxide. When a metalation time of 5 minutes was employed, the yields of acid at −25°, −30°, −35°, −37·5°, −40°, and −45° were 53, 62, 68, 72, 68, and 55% respectively: when the metalation was carried out at −40°, the yields of acid using a metalation time of 3·5, 5, and 6 minutes were 60, 68, and 58% respectively. Using the optimum conditions, *i.e.*, metalation at −38° for 5 minutes, we have thus obtained the acid in 73% yield.

The acid (IV) was converted into the acid chloride with thionyl chloride, and then cyclised in nitrobenzene, by using aluminium chloride, to 9-thia-3-aza-anthrone (V).

9-Thia-3-aza-anthrone (V), when heated with methyl toluene-*p*-sulphonate, readily undergoes quaternisation, and the methiodide and methochloride have thus been obtained. Attempts to oxidise the anthrone (V) to the sulphone failed, only intractable yellow oils being obtained: this result contrasts markedly with the ready and mild oxidation of the three isomeric 9-thia-aza-anthrones to their sulphones.

The nitration of the anthrone (V) gave one mononitro-derivative, m. p. 335°, in 66% yield, and an isomer, m. p. *ca.* 225°, in 17% yield: there is little doubt that these compounds are the 6- and the 8-nitro-derivatives (VI and VII) respectively, for nitration would occur more readily in the position *para* to the sulphur atom than in that *ortho* to this atom (cf. the corresponding products in the 2- and 4-aza-series). The very pale yellow 6-nitro-derivative (VI) on reduction gave the orange-yellow 6-amino-9-thia-3-aza-anthrone (VIII).

It is noteworthy that the 6-amino-derivatives of the 2- and 4-aza-anthrones are deep red, and evidence was adduced (Part IV) that this intense colour was due in each case to the contribution of a quadruply charged form in which the primary amine group and the sulphur atom become positively charged and the oxygen and the pyridyl nitrogen atom negatively charged: this is supported by the less intense colour of the 6-amino-derivative (VIII), which cannot show this extensive charge separation.

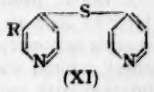
In earlier attempts to introduce the cyano-group into the pyridine ring before reaction with thiophenol, 4-hydroxy-3-nitropyridine (I; R = NO_2) was converted in turn into 3-amino-4-hydroxypyridine (I; R = NH_2) and 4-hydroxy-3-iodopyridine (I; R = I). Neither the amino- nor the iodo-compound could be converted into 3-cyano-4-hydroxypyridine (I; R = CN). Furthermore, many attempts using a variety of conditions to convert 4-hydroxynicotinic acid into 4-chloronicotinic acid (on the lines of our earlier syntheses) failed, the hydroxy-acid being either unchanged or, under more vigorous conditions, completely decomposed. Failure also attended the use, in the model experiments, of ethyl 4-chloro-2 : 6-dimethylnicotinate, which can be readily prepared from ethyl aminocrotonate (Michaelis and Arend, *Ber.*, 1901, **34**, 2284), for this chloro-group is unreactive and could not be condensed with thiophenol under various conditions.

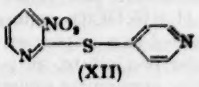
9-Oxa-3-aza-anthrone (X) has also been prepared, but the synthetic route remains unsatisfactory. 4-Chloro-3-nitropyridine (II) condensed smoothly with phenol to give 3-nitro-4-pyridyl phenyl ether (IX; R = NO_2); reduction then gave the 3-amino-derivative (IX; R = NH_2), which was converted into the 3-iodo-derivative (IX; R = I). The great instability of this iodo-derivative, even at room temperature, alone or in toluene solution, made the preparation of a lithio-derivative impracticable, and the synthetic route analogous to that employed for the thia-anthrone (V) had to be abandoned. The 3-amino-derivative (IX; R = NH_2) was therefore converted into 3-cyano-4-pyridyl phenyl ether (IX; R = CN), but the yield was very low, and all attempts to hydrolyse the nitrile to the acid caused decomposition. The cyano-derivative (IX; R = CN) when heated with sulphuric acid at 110° gave the carbamoyl derivative (IX; R = $CO{\cdot}NH_2$) but at 195° gave the required 9-oxa-3-aza-anthrone (X), both in very low yield, possibly owing to the formation of water-soluble sulphonated phenoxy-derivatives. A detailed investigation of the properties of the anthrone (X) could not therefore be undertaken.

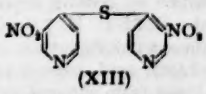
This conversion of an aromatic nitrile into a cyclic ketone is unusual, but Schaarschmidt (*Annalen*, 1915, **409**, 59) has shown that 1-cyano-2-*p*-tolylthioanthraquinone when heated with sulphuric acid undergoes a similar cyclisation to the corresponding thioxanthone.

Ultraviolet absorption data for 9-oxa-1-aza- and 9-oxa-3-aza-anthrone and the four isomeric 9-thia-aza-anthrones and various derivatives are given on p. 2761 and briefly discussed.

Certain pyridine derivatives prepared as intermediates for possible syntheses of 9-thia-diaza-anthrones, having the nitrogen atoms in different rings, are now recorded. 4-Chloro-3-nitropyridine (II) reacted with pyridine-4-thiol in boiling ethanol to give 3-nitro-4 : 4'-dipyridyl sulphide (XI; R = NO_2), but in acetone containing potassium carbonate to give 4 : 4'-dipyridyl sulphide (XI; R = H). The result recalls that of King and Ware (*J.*, 1939, 875), who found that pyridine-4-thiol reacted with bromine to give 4 : 4'-dipyridyl disulphide, but anomalously with chlorine to give the sulphide (XI; R = H). We find that the thiol reacted normally with 2-chloro-3-nitropyridine to give 3-nitro-2-pyridyl


(XI)


(XII)


(XIII)

4-pyridyl sulphide (XII). 3-Nitropyridine-4-thiol reacted with 4-chloro-3-nitropyridine (II) to form both di-3-nitro-4-pyridyl sulphide (XIII) and (in greater yield) the corresponding disulphide. Finally, a mixture of the pyridine (II) and 4-hydroxypyridine in boiling concentrated absolute ethanol solution gave 4-hydroxy-3-nitropyridine (I; R = NO_2) in 61% yield, a result which could hardly be due to simple hydrolysis. These reactions

warrant further investigation, particularly as only the main products were isolated in the above brief investigation.

Tests kindly undertaken by Mr. O. D. Standen at the Wellcome Laboratories of Tropical Medicine have shown that 9-thia-3-aza-anthrone (V) and its methochloride have no significant effect on schistosomiasis infections (cf. Part V). The introduction of the nitrogen atom into the four possible positions in the thioxanthone molecule has thus been without effect for this purpose.

Experimental

4-Hydroxy-3-nitropyridine (I; R = NO_2).—Pyridine was converted into 4-hydroxypyridine nitrate (Koenigs and Greiner, *Ber.*, 1931, **64**, 1049; Leis and Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 79). The nitrate (282 g.) was added to a mixture of fuming nitric acid (*d* 1·5) (570 g.) and 20% oleum (570 g.) which was warmed gently and, after the initial reaction had subsided, boiled for 1 hr. The cold mixture was poured with stirring into water (2 l.) and partly neutralised with ammonia. The precipitated yellow 4-hydroxy-3-nitropyridine (I; R = NO_2), when collected, washed, and dried (219 g., 88%), had m. p. 278—279°, and was sufficiently pure for the next stage : it crystallised readily from water (cf. Bremer, *Annalen*, 1937, **529**, 294). Koenigs and Fulde (*Ber.*, 1927, **60**, 2108) give m. p. 280—281°.

4-Chloro-3-nitropyridine (II).—Phosphorus oxychloride (9 c.c.) was added to an intimate mixture of the powdered hydroxy-pyridine (I; R = NO_2) (90 g.) and phosphorus pentachloride (150 g.), which was then heated in an oil-bath (120—130°) to ensure gentle boiling. When hydrogen chloride evolution ceased (*ca.* 3 hr.), distillation first removed the oxychloride at atmospheric pressure, and then gave the chloro-pyridine (II), a pale yellow liquid (83 g., 82%), b. p. 158°/25 mm., which solidified on cooling. Reitmann (*Med. u. Chem. Abh. med.-chem. Forschungsstätten I.G. Farbenind.*, 1934, **2**, 384; *Chem. Zentr.*, 1934, I, 3597) gives m. p. 45°, b. p. 95°/5 mm. The compound, which is lachrymatory and a strong skin-irritant, is stable if kept dry in a refrigerator.

3-Nitro-4-pyridyl Phenyl Sulphide (III; R = NO_2).—The chloro-pyridine (II) (3·1 g.) and thiophenol (2·1 g., 1 mol.) were mixed at *ca.* 10° and then cautiously warmed to *ca.* 20°; a violent exothermic reaction occurred and the mass solidified. This product melted at 185—190° with hydrogen chloride evolution, and was kept at 190—195° for 1 hr. until this decomposition was complete. The brown residual oil solidified on cooling, and when recrystallised from benzene and then aqueous ethanol furnished the *sulphide* (III; R = NO_2), yellow crystals, m. p. 86° (4·5 g.) (Found : C, 57·3; H, 3·6; N, 12·2. $C_{11}H_8O_2N_2S$ requires C, 56·9; H, 3·5; N, 12·1%).

3-Amino-4-pyridyl Phenyl Sulphide (III; R = NH_2).—Granulated tin (27 g.) was added to a suspension of the sulphide (III; R = NO_2) (22·8 g.) in concentrated hydrochloric acid (100 c.c.). On cautious heating, a vigorous reaction occurred, and the mixture was then heated on a water-bath for 30 min. The clear solution was strongly basified and the precipitated brown solid, when collected, washed, dried, and recrystallised from light petroleum (b. p. 60—80°), gave the *sulphide* (III; R = NH_2), cream-coloured needles, m. p. 107·5—108° (11·5 g., 58%) (Found : C, 65·3; H, 4·75; N, 13·6. $C_{11}H_{10}N_2S$ requires C, 65·3; H, 4·95; N, 13·8%).

3-Iodo-4-pyridyl Phenyl Sulphide (III; R = I).—A diazotised solution of the sulphide (III; R = NH_2) (8 g.) was added dropwise to an excess of potassium iodide in water at 75°. The deposited heavy brown oil, when collected, washed in turn with sodium hydroxide and thiosulphate solutions, and distilled, gave the sulphide (III; R = I) as a pale brown viscous syrup, b. p. 149°/0·03 mm. (slight decomp.) (8·9 g., 72%).

For characterisation, a sample was dissolved in an excess of warm aqueous 60% perchloric acid, which on cooling deposited the *perchlorate*, pale yellow leaflets, m. p. 189·5°, from water (Found : C, 32·2; H, 2·0; N, 3·5. $C_{11}H_8NIS,HClO_4$ requires C, 31·9; H, 2·2; N, 3·4%).

Aqueous chloroplatinic acid, when added to a suspension of another sample in concentrated hydrochloric acid, gave a yellow granular precipitate, m. p. 292° (decomp.), which, when recrystallised from ethanol–epichlorohydrin, apparently underwent co-ordination with reduction to bivalent platinum, forming *bis-(3-iodo-4-pyridyl phenyl sulphide)dichloroplatinum*, pale yellow rods, m. p. 164° (decomp.) (Found : C, 29·7; H, 2·0; N, 2·9; Pt, 22·0. $C_{22}H_{16}N_2Cl_2I_2S_2Pt$ requires C, 29·6; H, 1·8; N, 3·1; Pt, 21·9%).

3-Cyano-4-pyridyl Phenyl Sulphide (III; R = CN).—(*A*) A diazotised solution of the amine (III; R = NH_2) (2·5 g.) was added dropwise to a solution of cuprous cyanide in aqueous potassium cyanide at 75°. The brown precipitate was collected from the cooled mixture, dried,

and extracted with boiling ethanol. Evaporation of the filtered extract gave a dark brown gum, which, after repeated crystallisation from light petroleum (b. p. 60—80°), furnished the *nitrile* (III; R = CN), pale yellow crystals, m. p. 63—63·5° (0·45 g., 17%) (Found: C, 67·9; H, 3·7; N, 12·9. $C_{13}H_9N_2S$ requires C, 67·9; H, 3·8; N, 13·2%).

(*B*) An intimate mixture of the iodo-sulphide (III; R = I) (1 g.) and cuprous cyanide (3 g.), on heating, underwent no apparent change until 200°, when it darkened considerably. Extraction with boiling ethanol and recrystallisation as in (*A*) gave the nitrile (III; R = CN), m. p. and mixed m. p. 63°. The yield was very low.

The nitrile was unaffected when its suspension in 5% aqueous sodium hydroxide was boiled under reflux for 5 hr. Its solution in ethanolic potassium hydroxide, when boiled for 1 hr., evolved ammonia and then contained thiophenol. A mixture of the nitrile with concentrated hydrochloric acid or 90% sulphuric acid, when heated at 100° for 3 hr., liberated thiophenol, but the mixture yielded only a small amount of the unchanged nitrile.

3-Carboxy-4-pyridyl Phenyl Sulphide (IV).—(*a*) To prepare the solution of *n*-butyl-lithium, fine strips of very thin lithium foil (4 g.) and glass beads were added to a solution of *n*-butyl chloride (18·4 g.) in anhydrous toluene (200 c.c.) under nitrogen. The mixture was shaken for 24 hr., and then filtered under nitrogen pressure through a sintered glass funnel containing freshly heated "Hyflo Supercel." The concentration of the filtrate (which was stored under nitrogen) was determined by titration with standard acid. The yield was 64—69%. (*b*) A pre-cooled solution of the iodo-sulphide (III; R = I) (2·5 g.) in anhydrous toluene (10 c.c.) was rapidly added to the butyl-lithium solution (1·1 mols. of solute) which had been placed under nitrogen in a flask fitted with a mercury seal, and had been very vigorously stirred whilst being cooled to −38°. After 5 min., finely powdered carbon dioxide (*ca.* 5 g.) was added, and the stirring continued for 10 min. more. The mixture was poured into water, and the aqueous layer separated and treated with acetic acid until it attained pH 4. The precipitated yellow *acid* (IV) (1·45 g., 73%), when washed and dried, was sufficiently pure for the next stage: a sample, recrystallised in turn from ethanol and acetic acid, formed cream-coloured crystals, m. p. 236° (Found: C, 62·0; H, 4·05; N, 5·9. $C_{13}H_9O_2NS$ required C, 62·3; H, 3·9; N, 6·05%).

If the above acidification was carried out with 5N-hydrochloric acid, the *hydrochloride* of the acid was precipitated; it formed colourless crystals, m. p. 275° (decomp.), from ethanol (Found: C, 53·5; H, 3·6; N, 5·4. $C_{13}H_9O_2NS,HCl$ requires C, 53·8; H, 3·7; N, 5·2%).

Toluene was employed as a solvent in the above preparation because the iodo-sulphide (III; R = I) is insoluble in ether and light petroleum, and the use of benzene (cf. Ziegler and Colonius, *Annalen*, 1930, **479**, 135) was obviously precluded.

A sample of the acid (IV) was heated at 250° until effervescence ceased. The homogeneous melt, on cooling, formed an oil which did not solidify but, when treated with picric acid (both in ethanolic solution), gave *phenyl 4-pyridyl sulphide picrate*, yellow needles, m. p. 165°, from water (Found: C, 49·05; H, 3·05; N, 13·7. $C_{11}H_9NS,C_6H_3O_7N_3$ requires C, 49·0; H, 2·9; N, 13·5%).

9-Thia-3-aza-anthrone (V).—A mixture of the acid (IV) (9·1 g.) and thionyl chloride (30 c.c.) was boiled under reflux for 1 hr., the excess of chloride removed under reduced pressure, and the residue dissolved in dry nitrobenzene (50 c.c.), to which powdered aluminium chloride (13·5 g.) was then added. The mixture was heated at 100° for 3 hr., carefully poured on ice, and the nitrobenzene removed with steam. The filtered solution, when cooled and strongly basified with aqueous sodium hydroxide, deposited the *anthrone* (V) (7·45 g., 89%), which, when sublimed in a vacuum or crystallised from ethanol, formed colourless needles, m. p. 181° (Found: C, 67·7; H, 3·6; N, 6·75. $C_{13}H_7ONS$ requires C, 67·6; H, 3·3; N, 6·6%).

Quaternary salts. A mixture of the anthrone (V) (2 g.) and methyl toluene-*p*-sulphonate was heated at 170° for 4 hr., cooled, and repeatedly extracted with ether. An aqueous solution of the residue, when filtered and treated with an excess of aqueous potassium iodide, deposited the *methiodide* (2·5 g., 75%), yellow needles, m. p. 279·5—280°, from water (Found: C, 44·2; H, 3·0; N, 4·05. $C_{13}H_{10}ONIS$ requires C, 43·95; H, 2·85; N, 3·95%).

An excess of freshly prepared silver chloride was added to a solution of the methiodide (1 g.) in hot methanol (300 c.c.), which was boiled under reflux for 1 hr. whilst protected from the light. The hot mixture was filtered, the residue was washed with hot methanol, and the combined filtrate and washings were evaporated to small bulk, cooled, and diluted with a small volume of ether. The precipitated *methochloride monohydrate* (0·39 g., 49%), when recrystallised from methanol–ether, had m. p. 261·5° (efferv.) (Found: C, 55·4; H, 4·4; N, 4·9. $C_{13}H_{10}ONCl,H_2O$ requires C, 55·4; H, 4·25; N, 5·0%). The salt dissociates at its m. p. giving a residue of the pure anthrone (V), m. p. and mixed m. p. 180—181°.

Attempted oxidation. A suspension of the finely powdered anthrone (V) (1 g.) in acetic acid

(20 c.c.) was diluted with 30% hydrogen peroxide (4 c.c.) and kept at 70° for 5 hr. The addition of water precipitated unchanged anthrone (0·320 g.), and the only other product isolated was a water-soluble yellow oil which could not be purified. Closely similar results were obtained when this oxidation was performed at 90° for 2 hr., or at 20° for 2 or 14 days, and when the oxidation was attempted using chromic acid in acetic or in 10N-sulphuric acid, or potassium permanganate in acetone.

Nitration.—A mixture of the anthrone (1 g.), powdered sodium nitrate (0·5 g.), and sulphuric acid (100 c.c.) was kept at 35—40° with stirring for 10 min., and then poured on ice and neutralised with ammonia. The yellow precipitate was collected, washed, dried, and repeatedly extracted with boiling ethanol. The insoluble residue (0·80 g., 66%), when recrystallised from acetic acid, gave *6-nitro-9-thia-3-aza-anthrone* (VI), very pale yellow needles, m. p. 355° (Found: C, 55·85; H, 2·25; N, 11·3. $C_{13}H_6O_3N_2S$ requires C, 55·8; H, 2·3; N, 10·8%); it sublimed fairly readily at *ca.* 230°/0·002 mm.

The ethanolic extracts on evaporation gave the crude *8-nitro*-isomer (VII) (0·20 g., 16·5%), which was recrystallised from a minimum of ethanol so that the least soluble portion was discarded: after sublimation it melted rather indefinitely at 225° (Found: C, 55·6; H, 2·2; N, 11·1. $C_{13}H_6O_3N_2S$ requires C, 55·8; H, 2·3; N, 10·8%). The indefinite m. p. may indicate slight contamination by the 6-nitro-isomer, but there was insufficient material for further crystallisation: the infrared spectra of the two isomers were too similar to permit detection of a very small proportion of (VI) in (VII).

Stannous chloride (1·5 g.) was added to a solution of the 6-nitro-derivative (VI) (0·55 g.) in concentrated hydrochloric acid (10 c.c.), which was then kept at 60° for 1 hr. The cold mixture was strongly basified and the precipitated *6-amino-9-thia-3-aza-anthrone* (VIII) was collected, washed, dried, and heated at 225—230°/0·0005 mm., subliming very slowly to form orange-yellow prisms (0·42 g., 86%), m. p. 272—273° (Found: C, 63·9; H, 3·6; N, 12·7. $C_{13}H_8ON_2S$ requires C, 63·2; H, 3·5; N, 12·3%). Resublimation or recrystallisation from ethanol did not change the m. p.

3-Iodo-4-hydroxypyridine (I; R = I).—(*a*) Iron "pin-dust" (20 g.) was added in small portions to a warm stirred suspension of 4-hydroxy-3-nitropyridine (I; R = NO_2) (20 g.) in water (100 c.c.) containing concentrated hydrochloric acid (1 c.c.). When the main reaction had subsided, more pin-dust (30 g.) was added, and the mixture was heated for 30 min. on the water-bath, filtered hot, treated with an excess of hydrochloric acid, and evaporated to small bulk. The solution, on cooling, deposited crystalline 3-amino-4-hydroxypyridine hydrochloride (17·5 g., 84%) (cf. Crowe, *J.*, 1925, **127**, 2028). The free base readily decomposes, forming a coloured resin.

(*b*) A diazotised solution of this hydrochloride (7·8 g.) was added to an excess of aqueous potassium iodide, which was then gently warmed until effervescence ceased. The filtered solution, when neutralised with sodium hydrogen carbonate, deposited the *iodo*-compound (I; R = I) (3·25 g., 28%), colourless leaflets, m. p. 299—300° (decomp.), from water (Found: C, 27·6; H, 1·65; N, 6·35. C_5H_4ONI requires C, 27·2; H, 1·8; N, 6·3%).

3-Nitro-4-pyridyl Phenyl Ether (IX; R = NO_2).—A mixture of 4-chloro-3-nitropyridine (II) (7·2 g.) and phenol (15 g., 3·5 mols.) was heated under reflux until evolution of hydrogen chloride ceased (*ca.* 1 hr.), and was then cooled and poured into an excess of sodium hydroxide solution. The precipitated material solidified and, when collected, washed and recrystallised from aqueous ethanol or light petroleum (b. p. 40—60°), gave the colourless *nitro-ether* (IX; R = NO_2) (8·7 g., 89%), m. p. 74° (Found: C, 61·4; H, 3·9; N, 13·2. $C_{11}H_8O_3N_2$ requires C, 61·1; H, 3·7; N, 13·0%).

3-Amino-4-pyridyl Phenyl Ether (IX; R = NH_2).—Granulated tin (10·5 g.) was added to a solution of the ether (IX; R = NO_2) (6 g.) in concentrated hydrochloric acid (30 c.c.), which when gently warmed deposited a sticky cream-coloured solid: at *ca.* 35° a violent reaction ensued, and strong external cooling was applied. When the reaction subsided, the clear pale brown solution was heated at 100° for 1 hr., cooled, strongly basified, and repeatedly extracted with ether. The united extracts on distillation gave the amino-ether (IX; R = NH_2) as a pale yellow viscous syrup (4 g., 78%), b. p. 138°/0·2 mm., 145°/0·5 mm., which could not be obtained solid. In ethanol, it gave a *picrate*, yellow needles, m. p. 230°, from much ethanol (Found: C, 49·2; H, 2·8; N, 17·1. $C_{11}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 49·1; H, 3·1; N, 16·9%).

3-Iodo-4-pyridyl Phenyl Ether (IX; R = I).—The amino-ether (IX; R = NH_2) (23·7 g.) was diazotised, excess of nitrous acid removed with urea, and the solution then added as usual to aqueous potassium iodide. The heavy dark brown oil, when distilled in nitrogen, gave the iodo-ether (IX; R = I) (28 g., 75%) as a viscous brown syrup, b. p. 134°/0·03 mm. The syrup,

alone or in toluene solution, rapidly deposited a solid, which on crystallisation from ethyl acetate gave bronze-coloured leaflets, m. p. 155° : they were not identified, but may have been a *polyiodide* [Found : C, 27·2; H, 1·9; N, 3·1. $(C_{11}H_8ONI)_2I_2$ requires C, 27·1; H, 1·6; N, 2·9%].

The freshly prepared iodo-ether in ethanol solution, when added to aqueous chloroplatinic acid, gave a yellow precipitate insoluble in the common solvents : recrystallisation from epichlorohydrin caused co-ordination with the formation of *bis-(3-iodo-4-pyridyl phenyl ether)-tetrachloroplatinum*, yellow plates, m. p. 249° (dependent on rate of heating, considerable darkening at *ca.* 220°) (Found : C, 28·6; H, 2·1; N, 3·1; Pt, 21·0. $C_{22}H_{16}O_2N_2Cl_4I_2Pt$ requires C, 28·4; H, 1·75; N, 3·0; Pt, 21·0%).

3-Cyano-4-pyridyl Phenyl Ether (IX; R = CN).—The amino-ether (IX; R = NH_2) (2·8 g.), when diazotised and added to aqueous potassium cuprocyanide, gave the *nitrile* (IX; R = CN), which after sublimation at 100°/0·2 mm. and recrystallisation from ethanol formed colourless crystals (0·6 g., 21%), m. p. 104—105° (Found : C, 73·8; H, 4·4; N, 14·5. $C_{12}H_8ON_2$ requires C, 73·5; H, 4·2; N, 14·3%).

A suspension of this nitrile in 6N-hydrochloric acid, when boiled under reflux for 6 hr., gave a strong odour of phenol, but no other product could be isolated. A solution of the nitrile in ethanolic potassium hydroxide, when similarly boiled for 3 hr., evolved ammonia and gave an intractable dark resinous product.

3-Carbamoyl-4-pyridyl Phenyl Ether (IX; R = CO·NH_2).—A mixture of the nitrile (0·2 g.) and 95% sulphuric acid (2 c.c.) was heated at 110° for 90 min., cooled, diluted, and treated with an excess of aqueous ammonia. The precipitated *amide* (IX; R = CO·NH_2), when sublimed at 160°/0·005 mm., formed a colourless micro-crystalline powder (35 mg., 16%), m. p. 196° (Found : C, 67·6; H, 5·0; N, 12·6. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%).

9-Oxa-3-aza-anthrone (X).—The above mixture of nitrile and sulphuric acid was heated at 195° for 30 min., and the dark-brown reaction mixture, treated as before, deposited the *anthrone* (X), which after repeated sublimation at 160°/0·005 mm. formed white needles (20 mg., 10%), m. p. 184·5° (Found : C, 72·4; H, 3·8; N, 7·3. $C_{12}H_7O_2N$ requires C, 73·1; H, 3·6; N, 7·1%). A similar result was obtained when the mixture was heated at 165—170° for 3·5 hr.

Ultraviolet Absorption Spectra.—All were determined (see Table) in ethanol containing 5%

Xanthone	$\lambda_{max.}$	238 (38,700)	260 (11,900)	287 (4260)	336 (6300); $\lambda_{inf.}$ 232—233 (34,900)		
	$\lambda_{min.}$	212 (8390)	251 (8390)	281 (3860)	298 (930)		
Anthrone							
9-Oxa-1-aza-	$\lambda_{max.}$	226 (28,400)	276 (10,100)	282 (13,000)	332 (8000)		
	$\lambda_{min.}$	254 (6200)	277 (10,000)	298 (1640)			
9-Oxa-3-aza-	$\lambda_{max.}$	232—234 (40,000)		324 (5400); $\lambda_{inf.}$ 254—256 (11,990)			
	$\lambda_{min.}$	214 (17,100)		288 (1300)			
Thioxanthone	$\lambda_{max.}$	214 (5900)	219 (7400)	257 (18,900)	286 (2330)	299 (1590)	379 (2990)
	$\lambda_{min.}$	216 (5790)	225 (2690)	285 (2320)	295 (2450)	314 (166)	
Anthrone							
9-Thia-1-aza-	$\lambda_{max.}$	227 (25,800)	239 (24,000)	254 (34,350)	375 (6200)		
	$\lambda_{min.}$	220 (23,900)	235 (23,200)	242 (23,200)	309 (470)		
9-Thia-2-aza-	$\lambda_{max.}$	222 (17,000)	228 (16,800)	247 (19,900)	270 (16,900)	294 (6370)	304 (5870) 392 (6280)
	$\lambda_{min.}$	226 (16,600)	236 (13,700)	256 (14,200)	288 (5630)	300 (5360)	322 (240)
9-Thia-3-aza-	$\lambda_{max.}$	247 (31,800)	289 (8790)	299 (9400)	364 (5220)		
	$\lambda_{min.}$	230 (17,800)	283 (8500)	293 (8580)	318 (990)		
9-Thia-4-aza-	$\lambda_{max.}$	216 (11,900)	258 (37,300)	382–383 (5760)			
	$\lambda_{min.}$	222 (8300)	314 (390)				
9-Thia-1-aza-methiodide *	$\lambda_{max.}$	258 (14,800)	282 (16,000)	376 (5540)			
	$\lambda_{min.}$	249 (12,300)	267 (12,600)	330 (100)			
9-Thia-2-aza-methochloride	$\lambda_{max.}$	232 (31,000)	244 (18,300)	250 (17,200)	288 (11,600)	306 (9100)	420 (5060)
	$\lambda_{min.}$	240 (17,800)	249 (17,000)	270 (8160)	302 (9050)	344 (300)	
9-Thia-3-aza-methochloride *	$\lambda_{max.}$	234 (30,800)	276 (11,200)	335 (13,000); $\lambda_{inf.}$ 270—273 (11,100)			
	$\lambda_{min.}$	224 (24,200)	263 (10,900)	303 (4100)			
9-Thia-4-aza-methochloride	$\lambda_{max.}$	219 (18,700)	250 (13,000)	271 (28,500)	407—408 (2870)		
	$\lambda_{min.}$	232 (10,200)	254 (11,900)	340 (410)			
6-Amino-9-thia-3-aza	$\lambda_{max.}$	212 (18,200)	258 (35,200)	332 (7280)	424—429 (3370)		
	$\lambda_{min.}$	220 (13,700)	311 (5470)	375 (1370)			

of water except those marked *, which were determined in water. The λ values (in mμ) are followed by the ε values in parentheses.

It will be seen that all the spectra have a general similarity. They can however be separated

into two main groups. Xanthone and 9-oxa-1-aza- and 9-oxa-3-aza-anthrone form one group, in which there is usually a strong band in the 230-mμ, two weak contiguous bands at 260—280 mμ, and a marked band in the 335-mμ region. Thioxanthone and the four 9-thia-aza-anthrones form a second group, having usually one or two weak bands in the 220-mμ, a strong band in the 250—260-mμ, two weak bands in the 295—305-mμ, and a weak broad band in the 380-mμ region. The quaternary methohalides of the four 9-thia-aza-anthrones give absorption curves intermediate between the above two main types.

3-Nitro-4 : 4'-dipyridyl Sulphide (XI; R = NO_2).—Pyridine-4-thiol was prepared by King and Ware's method (*loc. cit.*). A solution of 4-chloro-3-nitropyridine (II) (3 g.) and the thiol (2 g., 1 mol.) in ethanol (50 c.c.) was boiled under reflux for 3 hr., then evaporated, and the residue treated with aqueous sodium hydroxide and extracted with ether. The dried extract was evaporated and the residue, when recrystallised from ether and then sublimed at 110°/0·01 mm., furnished the *sulphide* (XI; R = NO_2) (3·2 g., 77%), pale yellow needles, m. p. 112° (Found: C, 51·4; H, 3·2; N, 17·7. $C_{10}H_7O_2N_3S$ requires C, 51·5; H, 3·0; N, 18·0%).

The above experiment was repeated, the ethanol being replaced by acetone (50 c.c.) containing dry potassium carbonate (2·2 g.). The residue from the ether extract, when sublimed at 60°/0·005 mm. and then recrystallised from light petroleum (b. p. 40—60°), afforded 4 : 4'-dipyridyl sulphide (XI; R = H), (0·51 g.), pale cream crystals, m. p. 68° (Found ? C, 64·1; H, 4·4; N, 14·9. Calc. for $C_{10}H_8N_2S$: C, 63·8; H, 4·3; N, 14·9%). King and Ware (*loc. cit.*) give m. p. 71°.

Stannous chloride (1·05 g.) was added to a solution of the nitro-sulphide (XI; R = NO_2) (0·5 g.) in concentrated hydrochloric acid (10 c.c.), which was then heated at 60° for 1 hr., cooled, and strongly basified. The precipitate, when washed, dried, and sublimed at 140°/0·004 mm., afforded *3-amino-4 : 4'-dipyridyl sulphide* (XI; R = NH_2), colourless crystals, m. p. 138° (Found: C, 58·8; H, 4·8; N, 21·0. $C_{10}H_9N_3S$ requires C, 59·1; H, 4·45; N, 20·7%).

3-Nitro-2-pyridyl 4-Pyridyl Sulphide (XII).—A solution of 2-chloro-3-nitropyridine (0·40 g.) and the thiol (0·27 g., 1 mol.) in ethanol (10 c.c.) was boiled under reflux for 3 hr., and the solvent removed. The residue, when basified with aqueous sodium hydroxide solution, washed, and repeatedly sublimed at 145°/0·002 mm., afforded the *sulphide* (XII), yellow prisms (0·36 g., 63%), m. p. 144—145° (Found: C, 51·2; H, 2·9; N, 18·4. $C_{10}H_7O_2N_3S$ requires C, 51·5; H, 3·0; N, 18·0%).

3-Nitropyridine-4-thiol.—A solution of potassium hydroxide (7 g.) in methanol (40 c.c.) was saturated with hydrogen sulphide and rapidly added to one of 4-chloro-3-nitropyridine (9·10 g.) in methanol (100 c.c.). Heat was evolved and the solution became dark red. It was heated on a water-bath for 5 min., and the solvent removed under reduced pressure. A solution of the residue in water was acidified with acetic acid, and the precipitate, when recrystallised from ethanol, gave the above *thiol* (6·9 g., 70%), orange-yellow needles, m. p. 153° (effervescence) in a preheated bath (Found: C, 38·8; H, 2·35; N, 17·8. $C_5H_4O_2N_2S$ requires C, 38·5; H, 2·55; N, 17·95%). On slow heating, the substance melted indefinitely at 190—210°.

A solution of 4-chloro-3-nitropyridine (2 g.) and the thiol (2 g., 1 mol.) in ethanol (50 c.c.) was boiled under reflux for 90 min., a yellow deposit increasing steadily after the first 20 min. The solvent was removed, and the residue extracted first with aqueous sodium carbonate and then with boiling ethanol. The ethanolic extract on evaporation gave *di-3-nitro-4-pyridyl sulphide* (XIII), which after recrystallisation from a minimum of ethanol and then sublimation at 135—140°/0·0005 mm. formed yellow crystals (0·40 g., 11%), m. p. 129—130° (Found: C, 42·8; H, 2·0; N, 20·1. $C_{10}H_6O_4N_4S$ requires C, 43·1; H, 2·1; N, 20·1%).

The residue from the ethanol extraction was heated at 200°/0·001 mm., a yellow sublimate (0·9 g.) being slowly deposited, which had m. p. 210° after crystallisation from acetic acid (Found: C, 38·4; H, 2·5; N, 17·5%). The unsublimed residue (0·6 g.), recrystallised from ethyl acetate (charcoal), afforded *di-3-nitro-4-pyridyl disulphide*, colourless crystals, m. p. 235° from room-temperature, 240° when immersed at 230° (Found: C, 38·9; H, 2·1; N, 18·0. $C_{10}H_6O_4N_4S_2$ requires C, 38·7; H, 1·9; N, 18·1%). The identity of the yellow sublimate remains uncertain. Its composition is almost identical with that of the original thiol, from which it differs in its insolubility in ethanol. It is possible that it is the isomeric 3-nitropyrid-4-thione: Stevens, Beutel, and Chamberlin (*J. Amer. Chem. Soc.*, 1942, **64**, 1093) have recorded an apparently analogous case in which a substituted 2-hydroxypyridine and its tautomeric pyridone can each be isolated, and differ markedly in solubility in organic solvents.

In a different type of experiment, a mixture of 3-nitropyridine-4-thiol (0·5 g.), 2-bromopyridine (1 c.c.), and copper powder (10 mg.) was boiled under reflux for 15 min., and the excess of 2-bromopyridine then removed in a vacuum. The residue, when twice sublimed at

130°/0·0005 mm., furnished solely the yellow crystalline sulphide (XIII) (95 mg.), m. p. and mixed m. p. 131°.

A solution of 4-chloro-3-nitropyridine (5 g.) and 4-hydroxypyridine (3 g., 1 mol.) in absolute ethanol (60 c.c.), when boiled under reflux, became deep red: after 1 hour's heating the colour began to fade and a yellow deposit to form, the process being apparently complete after 3 hr. The deposit, when collected and recrystallised from water, afforded 4-hydroxy-3-nitropyridine (I; R = NO_2) (2·7 g., 61%), m. p. and mixed m. p. 279°. No other product was isolated from the mother-liquor.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 11th*, 1955.]

Studies in the Polyene Series. Part L. "Anhydrovitamin A_2."*

By H. B. HENBEST, E. R. H. JONES, T. C. OWEN, and V. THALLER.

[Reprint Order No. 6322.]

"Anhydrovitamin A_2" is shown to be an ethoxyanhydrovitamin A_1 (IV).

ACID-CATALYSED dehydration of vitamin A_1 (I) yields a crystalline hydrocarbon, $C_{20}H_{28}$, anhydrovitamin A_1. The structure (III) now accepted for this compound was put forward by Shantz, Cawley, and Embree (*J. Amer. Chem. Soc.*, 1943, **65**, 901) and by Meunier, Dubou, and Vinet (*Bull. Soc. chim. France*, 1943, **25**, 371), and has recently received powerful support from the studies of Oroshnik, Karmas, and Mebane (*J. Amer. Chem. Soc.*, 1952, **74**, 295) on the "retro"-group of dehydration products in the vitamin A_1 series.

Similar treatment of natural vitamin A_2 with hydrochloric acid in ethanol was reported by Shantz (*Science*, 1948, **108**, 417) to yield a crystalline compound, m. p. 89·5°, analysing for $C_{20}H_{26}$ or $C_{20}H_{28}$, named anhydrovitamin A_2. This exhibited ultraviolet light absorption almost identical with that shown by anhydrovitamin A_1, but with antimony trichloride in chloroform vitamin A_1 and its anhydro-compound gave solutions with $\lambda_{max.}$ 6200 Å whereas those of the corresponding A_2 compounds both exhibited $\lambda_{max.}$ 6930 Å—this difference originally led to the detection of vitamin A_2 in fish oils eleven years earlier (Edisbury, Morton, and Simpkins, *Nature*, 1937, **140**, 234; Gillam, Heilbron, Lederer, and Rosanova, *ibid.*, p. 133). Shantz (*loc. cit.*) also observed that seven mols. of hydrogen were absorbed by the anhydro-A_2 compound on microhydrogenation.

When the structure of vitamin A_2 (II) was elucidated by synthesis (Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657), it was confirmed that the vitamin was converted by ethanolic hydrochloric acid into a crystalline compound, m. p. 88°, exhibiting ultraviolet absorption identical with that shown by the anhydro-compound derived from the vitamin from natural sources. At this time the analytical data reported earlier for the dehydration product were accepted, and a structure (V) was proposed tentatively in a preliminary communication (*Chem. and Ind.*, 1951, 49).

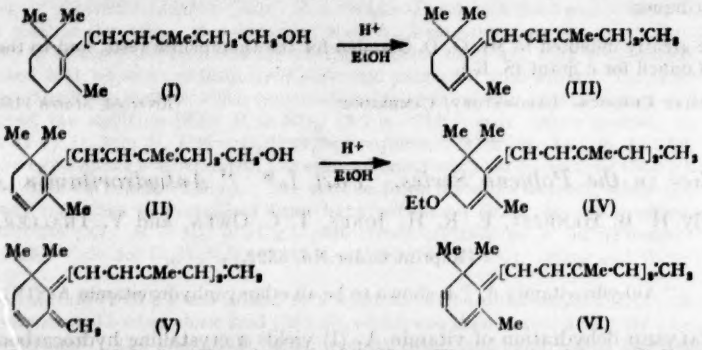
Later, the infrared spectrum of the compound was determined, and it was found difficult to reconcile the presence of a very strong band near 1100 cm.$^{-1}$ with a hydrocarbon structure. Further study has now shown that the compound contains an alkoxyl group derived from the alcohol in which the reaction is carried out. Thus, "anhydrovitamin A_2" is really 4'-ethoxyanhydrovitamin A_1 (IV), and use of methanol as reaction medium afforded the analogous methoxy-compound.

The new structure explains the close similarity between the ultraviolet absorption of the compounds (III) and (IV), closer agreement of ε values now being observed with the increased contribution from the molecular weight of the A_2-compound. The relatively strong band at 1100 cm.$^{-1}$ present in the infrared spectrum of (IV) [but not shown by (III)] is now readily explained as a C–O stretching frequency. The earlier hydrogenation

* Part XLIX, *J.*, 1953, 2125.

results may be reinterpreted by assuming that hydrogenolysis of the allylic C–O bond occurs, and the new formula also explains the ease of chromatographic separation of the two anhydro-compounds, whereas the parent alcohols are virtually inseparable (cf. Embree and Shantz, *J. Biol. Chem.*, 1940, **132**, 619).

The different course of reaction of the two vitamins upon treatment with dilute mineral acid may be interpreted as follows. In both the A_1- and the A_2-series, initial removal of



a hydroxyl group with its bonding electrons should readily occur to give an allylic carbonium ion. In the A_1-series this loses a proton to the medium, yielding a hydrocarbon with a "retro"-structure, the ready formation of which indicates that this arrangement of double bonds represents a relatively stable, unstrained molecular structure. In the A_2-series, stabilisation by loss of a proton would most likely generate structure (V) or (VI). Compared with the analogues (III) or (IV), these would be expected to be strained owing to the enforced coplanarity of the terminal ring, which will cause increases in the internal bond angles of the singly linked carbon atoms. Reaction of the intermediate carbonium atom with solvent therefore takes place to give the unstrained "retro-ether" structure (*e.g.*, IV).

The reaction of anhydrovitamin A_1 with *N*-bromosuccinimide has also been studied as a possible route to compounds of a true anhydrovitamin A_2 structure (*e.g.*, V or VI). Reaction between the hydrocarbon and the bromo-imide occurred readily, even at −40°; the product at this stage showed little characteristic ultraviolet absorption and the presence of carbonyl bands in the infrared spectrum indicated that addition of reagent to the polyene system was the major reaction. However, if the reaction product was treated with *N*-phenylmorpholine some unsaturated hydrocarbon (~5%) could be isolated, and this on further chromatography gave a fraction exhibiting a main absorption maximum at 4080 Å, with subsidiary maxima at 3870 and 4330 Å. The absorption data are not inconsistent with the dehydro-structure (VI), but the small yield (1%) of this compound and its great sensitivity to oxygen rendered further investigation unattractive.

Experimental

General directions are as given in Part XLIII (*J.*, 1952, 2557).

4'-Ethoxyanhydrovitamin A$_1$ (IV).—A solution of vitamin A_2 (0·35 g.) (prepared as in the following paper) in ethanol (5 c.c.) was treated with anhydrous ethanolic hydrogen chloride (40 c.c.; M/30). After being kept at 20° for 20 min., the mixture was poured into water, and the product isolated with pentane, and then chromatographed on alumina (200 g.). Elution with pentane (400 c.c.) afforded a golden-yellow oil (0·2 g.) which was dissolved in pentane (2 c.c.) and filtered through alumina (0·1 g.) into a small tube. This was sealed with a bung, cooled to −30°, and then allowed to warm to −10°. During 2 days a crystalline product separated. The supernatant liquid was decanted and the material crystallised twice in a similar manner, to give the *ethoxy-compound* as thick yellow needles, m. p. 86—88° (Found: C, 84·55; H, 10·35; OEt, 14·5. $C_{32}H_{50}O$ requires C, 84·55; H, 10·3; OEt, 14·4%). Ultraviolet absorption: $\lambda_{max.}$ 3520, 3700, and 3910 Å (ε 63,800, 95,000, and 85,600 respectively).

Infrared spectrum: peaks at 2980, 2940, 2870, 1450, 1362, 1200, 1085, 1102, 985, 968, and 885 cm.$^{-1}$.

The *methyl ether*, prepared similarly, had m. p. 76—77° (Found: C, 84·4; H, 10·35; OMe, 10·7. $C_{21}H_{30}O$ requires C, 84·5; H, 10·15; OMe, 10·4%).

Reaction of Anhydrovitamin A_1 with N-Bromosuccinimide.—*N*-Bromosuccinimide (0·858 g., 1·18 mol.) was added to a stirred solution of the hydrocarbon (1·09 g.) in chloroform (25 c.c.; freshly distilled from P_2O_5) at −45° in a nitrogen atmosphere. The solution was warmed to −20° during 30 min. *N*-Phenylmorpholine (2·2 g.) was then added. The mixture was heated under reflux for 2 min., cooled, poured into dilute hydrochloric acid, and extracted with light petroleum. After the usual processing the organic extract was evaporated under reduced pressure. The tarry residue was extracted with light petroleum; the soluble material (62 mg.) showed $\lambda_{max.}$ 3700 and 4070 Å. Chromatography on alumina (150 g.; P. Spence, grade O) with light petroleum as developing solvent gave three yellow zones. The most readily eluted showed $\lambda_{max.}$ 3700 Å, the next showed $\lambda_{max.}$ 3700 and 4080 Å, and the last exhibited $\lambda_{max.}$ 3870, 4080, and 4330 Å. All of these fractions were orange, very oxygen-sensitive gums.

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THE UNIVERSITY, MANCHESTER, 13. [*Received, April 12th*, 1955.]

Studies in the Polyene Series. Part LI. Conversion of Vitamin A_1 into Vitamin A_2.*

By H. B. HENBEST, E. R. H. JONES, and T. C. OWEN.

[Reprint Order No. 6323.]

A method for converting vitamin A_1 into vitamin A_2 has been devised which makes the latter readily accessible. Crystalline vitamin A_1 acid nitrile is also described.

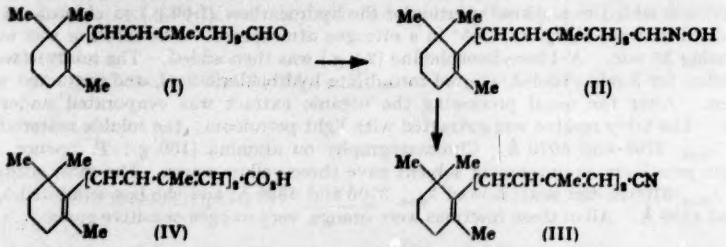
WHEN the structural problem of "anhydrovitamin A_2" was reinvestigated a supply of vitamin A_2 was required. The difficulty of obtaining the pure vitamin from natural sources and the considerable length of the synthesis (from β-ionone) employed to establish its structure (Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657) led to the consideration of other routes. Since vitamin A_1 acid (IV) was an intermediate in the previous synthesis the conversion of (commercially available) vitamin A_1 acetate into this acid was investigated, but various attempts to oxidise the vitamin itself or to oxidise further the corresponding aldehyde retinene$_1$ (I) were abortive. However, an indirect oxidation of retinene$_1$ was accomplished by dehydration of its oxime (II) with phosphorus oxychloride in pyridine to yield vitamin A_1 acid nitrile (III). This was obtained crystalline, exhibited $\lambda_{max.}$ 3580 Å in the ultraviolet region, and gave a C≡N stretching frequency (2210 cm.$^{-1}$) in the expected position in the infrared spectrum. However, hydrolysis to the acid by dilute alkali proceeded extremely slowly and use of more drastic conditions led to much decomposition, thus rendering this route to the acid impracticable. The difficulty encountered with the hydrolysis step is probably connected with delocalisation of the charge separation in the nitrile group by conjugation with the extended unsaturated system, the effect being augmented by hyperconjugation with attached alkyl groups.

Introduction of the extra double bond in the terminal ring in the previous A_2 synthesis was carried out on the methyl ester of the acid (IV), bromination with *N*-bromosuccinimide being followed by treatment with *N*-phenylmorpholine. Vitamin A_1 acetate reacted readily with *N*-bromosuccinimide, but allylic attack appeared to take place at either end of the

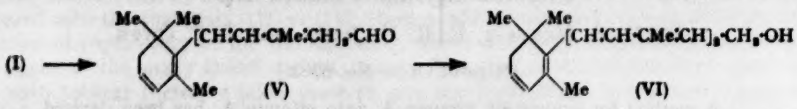
* Part L, preceding paper.

unsaturated system, for the light-absorption properties of the product obtained after dehydrobromination indicated the presence of a mixture of vitamin A_1 and A_2 acetates and the two retinenes.

Trial experiments (with benzaldehyde) had shown that an aldehyde group does not



react readily with *N*-bromosuccinimide, and this offered promise for bromination of retinene$_1$ (I) at the allylic position in the terminal ring. Under carefully controlled conditions (see Experimental section) this reaction proceeded smoothly, to yield an unstable bromo-compound, which on dehydrobromination afforded retinene$_2$ in more than 60% overall yield. The retinene$_2$ obtained was clearly a mixture of two or more stereoisomers for although it showed an ultraviolet absorption almost identical with that of the crystalline (all-*trans*-)aldehyde, it could not be induced to crystallise satisfactorily even after careful chromatography. The all-*trans*-form was, however, the chief isomer present for it could be separated as its oxime (30% overall yield from retinene$_1$) by treatment of the mixture with hydroxylamine acetate. The formation in the bromination–dehydrobromination



procedure of a mixture of geometrical isomers starting with crystalline all-*trans*-retinene$_1$ parallels our previous observations in the C_{20} ester series where a high yield of spectroscopically pure dehydro-ester was obtained from crystalline A_1-ester, but from which only a 30% yield of crystalline all-*trans*-acid was obtained on hydrolysis. The interconversion of isomers probably occurs during the bromination; an intermediate complex radical or ion may be produced, which by resonance stabilisation with the unsaturated system may cause the ultimate formation of new geometrical arrangements in the side-chain.

Reduction of retinene$_2$ (stereoisomeric mixture) by lithium aluminium hydride yielded vitamin A_2, characterised as in the earlier work by its ultraviolet absorption spectrum, preparation of a *p*-phenylazobenzoate, and by conversion into crystalline "anhydrovitamin A_2." This route to vitamin A_2 is the first based on vitamin A_1, and provides a more convenient route to the rarer vitamin.

Experimental

1-Cyano-2 : 6-dimethyl-8-(2 : 6 : 6-trimethylcyclohex-1-enyl)octa-1 : 3 : 5 : 7-tetraene (III).—Phosphorus oxychloride (0·25 c.c.) in pyridine (1 c.c.) was added to a solution of retinene$_1$ oxime (200 mg.) in pyridine (2 c.c.) cooled to −70°. On being allowed to warm to 0° the solution became deep red. The product was then isolated with light petroleum and chromatographed on alumina. The most easily eluted material was crystallised from methanol to give the *nitrile* (70 mg.) as yellow prisms, m. p. 50—50·5° (Found: C, 85·0; H, 9·45. $C_{20}H_{27}N$ requires C, 85·35; H, 9·6%). Ultraviolet spectrum (in EtOH): $\lambda_{max.}$ 3580 Å (ε = 47,200). Infrared spectrum: strong bands at 965, 1580, 2210, and 2920 cm.$^{-1}$.

Conversion of Retinene$_1$ into Retinene$_2$ (V).—Retinene$_1$ (2·2 g.) was dissolved in dry chloroform (50 c.c.; freshly distilled from P_2O_5) at 0°, and finely powdered *N*-bromosuccinimide (1·6 g.) was added with vigorous stirring. After 10 min. dissolution of the bromo-imide was complete

and a dark brown colour developed. Stirring was continued for a further 5 min. and *N*-phenylmorpholine (2 g.) was then added. The solution was heated under reflux for 5 min. and then poured into dilute hydrochloric acid, and the polyene isolated with pentane. Chromatography on deactivated alumina (400 g.) gave a main orange band which was eluted with pentane–ether (50 : 1) to give retinene$_3$ (1·4 g.), $\lambda_{max.}$ 4000 Å (ε = 35,000); the infrared spectrum was almost identical with that of the crystalline material. Further chromatography and fractional separation from cold pentane failed to give satisfactory crystalline material. The non-crystalline retinene$_3$ (1·4 g.) was converted into its oxime (cf. *J.*, 1952, 2657). The crude crystalline oxime (0·78 g.) gave on crystallisation from methanol the pure oxime as orange needles, m. p. 147—148° (Found: C, 81·0; H, 9·1. Calc. for $C_{20}H_{27}ON$: C, 80·75; H, 9·15%). M. p. given in our previous paper, 141—143°.

Vitamin A$_3$ (VI) *and its* p-*Phenylazobenzoate.*—Finely powdered lithium aluminium hydride (0·3 g.) was added to a solution of retinene$_3$ (0·75 g.; stereoisomeric mixture prepared as in the previous experiment) in dry ether (30 c.c.) at −30°. The mixture was kept at −30° for 30 min. with occasional agitation. Ethyl acetate was then added, and the vitamin isolated with ether and chromatographed on deactivated alumina (200 g.). Two minor products were eluted with pentane, and the main band was then eluted with ether, to give the vitamin (0·52 g.) as a yellow oil, extremely reactive to oxygen. It was dissolved in methylene dichloride (0·8 c.c.) and pyridine (0·8 c.c.); *p*-phenylazobenzoyl chloride (0·6 g.) was added and the mixture was shaken for 4 hr. Ether was added and the *p*-phenylazobenzoic anhydride filtered off. The solution was washed with dilute acid and dilute alkali, and the product chromatographed on deactivated alumina (200 g.). The single orange band was eluted with light petroleum to afford an orange oil (0·55 g.) which was dissolved in pentane (3 c.c.) and kept at −5° for 72 hr. The solid product was crystallised several times from pentane at −5°, to give vitamin A$_3$ *p*-phenylazobenzoate (0·2 g.) as thick orange-red needles, m. p. 74—77° (Shantz, *loc. cit.*, records m. p. 76—77°.).

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The Epimeric (±)-3-*Aminocyclohexanecarboxylic Acids.*

By F. R. HEWGILL and P. R. JEFFERIES.

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cis- and *trans*-3-Amino*cyclo*hexanecarboxylic acids have been prepared by a stereochemically specific method. A cyclic lactam (II) has been reduced to 1-aza*bicyclo*[3 : 2 : 1]octane (IV). The first dissociation constants of the amino-acids have been determined.

BAUER and EINHORN (*Annalen*, 1901, **319**, 329) obtained a 3-amino*cyclo*hexanecarboxylic acid of m. p. 268—269°, and a similar product, m. p. 268°, was described by Orthner and Hein (*Biochem. Z.*, 1933, **262**, 461), but in neither case did the authors make a configurational assignment. More recently, Greenstein and Wyman (*J. Amer. Chem. Soc.*, 1938, **60**, 2341) prepared crystalline samples of the amino-acid by platinum-catalysed hydrogenation of *m*-aminobenzoic acid in acid and in neutral solution, giving products, m. p. 264° and 278° respectively, which they considered to be identical. The last authors, by comparison of the dielectric increments of the 2-, 3-, and 4-amino*cyclo*hexanecarboxylic acids plotted against the mean-square distances separating the charged groups with the straight line obtained for this function of the simple aliphatic amino-acids, concluded that the 2- and 4-amino-acids probably occur in the *cis*-configuration, and the 3-isomer in the *trans*-configuration. They recognised that their arguments were somewhat artificial but apparently did not consider the possibility that their preparations were epimeric mixtures. Moreover, they made no mention of the work of Orthner and Hein (*loc. cit.*) who clearly described the preparation of both geometrical isomers of 4-amino*cyclo*hexanecarboxylic acid. Similar preparations have since been described by Wendt (*Ber.*, 1942, **75**, 425), and by Ferber and Brückner (*Ber.*, 1943, **76**, 1019), and Hünig and Kahanek (*Ber.*, 1953, **86**, 518) have prepared both *cis*- and *trans*-2-amino*cyclo*hexanecarboxylic acids. These results, taken in conjunction with the usual steric course of catalytic hydrogenation (Barton, *J.*, 1953, 1029; Bose, *Experientia*, 1953, **9**, 256), suggest that Greenstein and

Wyman's 2- and 4-amino-acids are epimeric mixtures richer in the *trans*-epimer, while their 3-isomer is probably a mixture richer in the *cis*-epimer, *i.e.*, the configurations are the reverse of those suggested by them.

It appeared possible to clarify the matter in the case of the 3-amino-acid by applying the Schmidt reaction, found to proceed with retention of molecular configuration and asymmetry by Campbell and Kenyon (*J.*, 1946, 25) in their particular case, to the epimeric hexahydro*iso*phthalic acids, the configurations of which have been established with certainty by resolution of the *trans*-acid (Böeseken and Peek, *Rec. Trav. chim.*, 1925, **44**, 845), and by anhydride formation from the *cis*-acid (Baeyer and Villiger, *Annalen*, 1893, **276**, 261; Goodwin and Perkin, *J.*, 1905, **87**, 841). If both epimers of the amino-acid are stable each should be formed stereochemically pure from the appropriate epimer of hexahydro*iso*phthalic acid.

In an attempt to obtain greater selectivity we used methyl hydrogen *cis*-hexahydro*iso*-phthalate with one equivalent of sodium azide, for hydrazoic acid appears to react more readily with carboxyl than with alkoxycarbonyl groups (Smith, "Organic Reactions," Vol. 3, p. 364). No amino-ester could be isolated, however, the product being identified through its benzoyl derivative as the amino-acid itself. The absence of the amino-ester may be explained either by assuming that in this case hydrazoic acid reacts more readily with the methoxycarbonyl group, or more probably by the extreme ease with which many esters are hydrolysed in concentrated sulphuric acid (Gillespie and Leisten, *Quart. Reviews*, 1954, **8**, 40).

Best yields (80%) of the amino-acid were obtained by slow addition of hydrazoic acid in chloroform to a sulphuric acid solution of the hexahydro*iso*phthalic acid itself. The use of hydrazoic acid rather than sodium azide was necessitated both by the greater control over the rate of addition and by the subsequent method of isolation. As the reaction was rather slow, the possibility of isomerisation was ruled out by blank experiments in which the hydrazoic acid was omitted. The characteristics of the two epimeric 3-amino*cyclo*-hexanecarboxylic acids so obtained from the corresponding hexahydro*iso*phthalic acids are shown below.

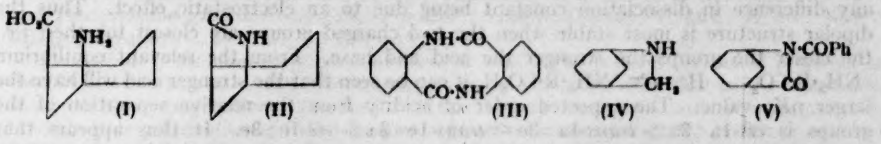
	M. p., *cis*	M. p., *trans*
3-Amino*cyclo*hexanecarboxylic acid	284°	290—291°
Benzoyl derivative	166—167	195—196
p-Bromophenacyl ester of the benzoyl derivative	211—212	182
α-Naphthylcarbamoyl derivative	207	213—214

Benzoylation of the amino-acid obtained by platinum-catalysed hydrogenation of *m*-aminobenzoic acid in acid solution gave a derivative identical with that obtained from the Schmidt reaction on methyl hydrogen *cis*-hexahydro*iso*phthalate and on the acid itself. Confirmation is thus provided for the suggested reversal of configuration of the 3-amino*cyclo*hexanecarboxylic acid prepared by Greenstein and Wyman.

Further evidence that the configurations assigned to these 3-amino-acids on the basis of the stereochemical specificity of the Schmidt reaction are correct was provided by formation of the lactam (II). The two substituents in the diaxial conformation of the *cis*-amino-acid (I) are favourably situated for the elimination of water, and pyrolysis of the *cis*-amino-acid gave a 30% yield of a lactam. However, the same lactam was obtained in 13% yield by pyrolysis of the *trans*-amino-acid. That the lactam is derived from the *cis*-amino-acid was proved by hydrolysis with barium hydroxide, which afforded only this acid. Orthner and Hein (*loc. cit.*) observed a similar partial isomerisation in the formation of the lactam of 4-amino*cyclo*hexanecarboxylic acid, but this could not be verified by Wendt (*loc. cit.*).

A complication arose in that the molecular weight (Rast's method) of the lactam was almost double that required by (II). As the dipeptide (III) had been described by Mazza (*Chem. Abs.*, 1939, **33**, 2957), the possibility of a bimolecular structure had to be considered. Inspection of models showed that dipeptide formation from either epimer in the 3-amino-series was only possible from a pair of diaxially substituted amino-acids involving considerable steric hindrance. To establish the unimolecular structure of the lactam experimentally, the latter was reduced with lithium aluminium hydride by the method of Ruzicka,

Kobelt, Häfliger, and Prelog (*Helv. Chim. Acta*, 1949, **32**, 544) to a crystalline base. The molecular weights of both the α-naphthylurethane and the *p*-nitrobenzoyl derivative closely correspond to those for derivatives of 6-aza*bicyclo*[3 : 2 : 1]octane (IV). Further evidence that the lactam possesses the unimolecular structure (II) was provided by pyrolysis of *cis*-3-benzamido*cyclo*hexanecarboxylic acid, which gave the *N*-benzoyl derivative (V), the molecular weight of which corresponded to the structure shown. Although



(I) (II) (III) (IV) (V)

some benzoic acid was obtained from this pyrolysis, none of the lactam itself could be isolated. The bimolecular association shown by the lactam in solution in camphor is probably attributable to hydrogen bonding between the very favourably situated atoms. Ferber and Brückner (*loc. cit.*) report a similar phenomenon with the lactam of 4-amino-*cyclo*hexanecarboxylic acid.

The reversal of the Auwers–Skita rule for 1 : 3-disubstituted *cyclo*hexanes (Pitzer *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 977, 2488; *Science*, 1947, **105**, 647; Hassel *et al.*, *Acta Chem. Scand.*, 1947, **1**, 929; 1950, **4**, 597) implies that in general the m. p.s of *cis*-1 : 3-compounds should be higher than those of their *trans*-epimers. From the foregoing Table it can be seen that for 3-amino*cyclo*hexanecarboxylic acid and its derivatives this condition is fulfilled in only one instance. A similar situation exists for *cyclo*hexane-1 : 3-diol where the *cis*-epimer has the lower m. p. (Rigby, *J.*, 1949, 1586, 1588). Although m. p.s are the least reliable criteria for the application of the Auwers–Skita rule, and the m. p.s of amino-acids are as a rule merely temperatures of decomposition, we found these two exceptions suggestive. Kuhn (*J. Amer. Chem. Soc.*, 1952, **74**, 2492) has provided firm evidence that *cis-cyclo*hexane-1 : 3-diol is stabilised in the diaxial conformation by hydrogen bonding, a possibility suggested by Hassel and Ottar (*loc. cit.*, 1947), and as the physical properties with which the rule is concerned appear to depend largely on the compactness of the molecule, it seemed possible that the discordant m. p.s in the case of the 3-amino-acid might arise from a similar cause.

From the high m. p.s and extreme insolubility in organic solvents, and by analogy with aliphatic amino-acids, these 3-amino*cyclo*hexanecarboxylic acids must be assumed to be largely in the form of dipolar ions. Consequently, the attraction between the oppositely charged groups might be expected to hold the *cis*-amino-acid in the diaxial conformation, overcoming the destabilisation due to steric factors. Empirically it is improbable that this destabilisation would seriously exceed the 6 kcal./mole calculated for the diaxial form of *cis*-1 : 3-dimethyl*cyclo*hexane (Pitzer and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 977), since it is known that the methyl is more effective than the carboxyl group in hindering the rotation of diphenyls. Albrecht and Corey (*ibid.*, 1939, **61**, 1087) have shown that in crystalline glycine the nitrogen atom is separated from the oxygen atoms of a carboxyl group in the same plane by 2·76 and 2·88 Å. These distances may be compared with a value of 2·8 Å in the diaxial form where the nitrogen atom is equidistant from the two oxygen atoms. For the vapour phase, where the effective dielectric constant will be approximately unity, simple calculation gives an electrostatic stabilisation energy of approximately 70 kcal./mole for the diaxial form, which would thus be expected to be the more stable form. In solution, however, the evaluation of effective dielectric constants (Kirkwood and Westheimer, *J. Chem. Phys.*, 1938, **6**, 506; Sarmousakis, *ibid.*, 1944, **12**, 277) is complicated by the choice of suitable models.

The first dissociation constants of the epimeric amino-acids were therefore determined by using a glass electrode and Tague's method of correction for the solvent (*ibid.*, 1920, **42**, 173). The pK_1 values of 3·70 and 3·85 obtained for the *cis*- and the *trans*-epimer respectively at 15° are close to those obtained for the crude 3- and epimeric 4-amino*cyclo*hexane-carboxylic acids (Orthner and Hein, *loc. cit.*; Greenstein and Wyman, *loc. cit.*), and are

considerably larger (*ca.* 1 pK unit) than those found by these authors for crude 2-aminocyclohexanecarboxylic acid. On these grounds alone it appears unlikely that the *cis*-3-amino-acid is stabilised in the diaxial form in aqueous solution. If the difference of 0·15 in the pK_1 values for the isomeric acids is significant the following argument may be applied. As the two charged groups are separated by the same number of carbon atoms in each geometrical isomer, the inductive effect may be assumed to be the same in both isomers, any difference in dissociation constant being due to an electrostatic effect. Thus the dipolar structure is most stable when the two charged groups are closest together, *i.e.*, the closer the groups the stronger the acid and base. From the relevant equilibrium $^+NH_2{\cdot}R{\cdot}CO_2^- + H^+ \rightleftharpoons {}^+NH_2{\cdot}R{\cdot}CO_2H$, it can be seen that the stronger acid will have the larger pK_1 value. The expected order of acidity from the relative separation of the groups is *cis*-1a : 3a > *trans*-1a : 3e ≏ *trans*-1e : 3a > *cis*-1e : 3e. It thus appears that the *cis*-epimer, being the weaker acid, is more stable in the diequatorial form in solution. Further evidence for this conclusion is provided by Greenstein and Wyman's observation (*loc. cit.*) that, if the attraction of oppositely charged groups could give rise to conformations of lower energy content, the dielectric increment found for the 2-amino-acid should not be less than that for the 3- and 4-isomers, whereas in fact it is.

Experimental

cis- and *trans*-Hexahydro*iso*phthalic acids were prepared as described previously (*J.*, 1954, 700) with the exception that hydrogenation was carried out at 70° under an initial pressure of 1000 lb./sq. in. The hydrogenations were then usually complete in 3 hr., and the proportion of the *trans*-epimer produced was only slightly less than that obtained under atmospheric conditions. Both epimers were recovered stereochemically pure after stirring their solutions in sulphuric acid with chloroform for 6 hr. at 60°.

Solutions of hydrazoic acid in chloroform, obtained as described in "Organic Reactions" (1946, Vol. 3, p. 327), were analysed by titration with standard alkali; they showed no sign of deterioration after 6 months' storage over anhydrous sodium sulphate at 0°. The usual safety precautions were adopted.

Hydrogenation of m-*Aminobenzoic Acid.*—*m*-Aminobenzoic acid (7 g.), four times recrystallised from water, was hydrogenated exactly as described by Greenstein and Wyman (*loc. cit.*). The reaction was stopped when the theoretical amount of hydrogen had been absorbed. Three precipitations of the crude 3-amino*cyclo*hexanecarboxylic acid (4·6 g.) from aqueous solution by acetone gave microcrystals, m. p. 279° (decomp.). Benzoylation of this product in aqueous sodium carbonate, followed by recrystallisation from chloroform–hexane, gave 3-*benzamido*-cyclo*hexanecarboxylic acid* (50%) as prisms, m. p. 166—167° (Found: C, 68·3; H, 6·7; N, 5·6. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%). Recrystallisation from aqueous ethanol gave plates, m. p. 167—168°.

cis-3-*Amino*cyclo*hexanecarboxylic Acid.*—(a) *From* cis-3-*methoxycarbonyl*cyclo*hexanecarboxylic acid.* The methoxy-acid, b. p. 136—140°, m. p. 59—60°, was prepared (see Vavon and Peignier, *Bull. Soc. chim.*, 1929, **45**, 300) from the anhydride of *cis*-hexahydro*iso*phthalic acid. Powdered sodium azide (0·5 g.) was added portionwise (90 min.) to a well-stirred solution of this *cis*-monoester (1·3 g.) in chloroform (30 ml.) and concentrated sulphuric acid (5 ml.), kept at 40°. The temperature was then raised to 50°, and stirring continued for a further 30 min. When cool, the mixture was poured on crushed ice and separated. Evaporation of the chloroform gave a negligible residue. The solution was made just alkaline with sodium hydroxide and continuously extracted with ether: however, no residue was obtained on evaporation of the dried ($MgSO_4$) ethereal extract. The solution was then made neutral to phenolphthalein with sulphuric acid and concentrated to *ca.* 40 ml. under reduced pressure. Ethanol (15 ml.) was carefully added to this warm solution, and after two days the precipitated sodium sulphate was filtered off. The filtrate was evaporated to dryness under reduced pressure and the solid residue, which appeared to be almost free from sodium sulphate, was benzoylated as described above. Recrystallisation from aqueous ethanol gave plates, m. p. 165—166°, mixed m. p. with the benzoyl derivative of the amino-acid obtained by hydrogenation 166—167°.

(b) *From* cis-*hexahydroisophthalic acid.* A solution of hydrazoic acid in chloroform (8·4%; 20·3 ml.) was added dropwise (75 min.) to a well-stirred mixture, at 35°, of chloroform (60 ml.) and a solution of *cis*-hexahydro*iso*phthalic acid (6 g.) in concentrated sulphuric acid (18 ml.).

Stirring was continued at 40° for 75 min., and finally at 50° for 30 min., evolution of nitrogen then having practically ceased. When cool, the layers were separated. Evaporation of the chloroform left no residue. The sulphuric acid layer was diluted with ice (60 g.), and a solution of crystalline barium hydroxide (120 g.) added. Dilute sulphuric acid was added dropwise to the filtrate until the barium was removed quantitatively. Concentration of the filtered solution under reduced pressure to *ca.* 30 ml., followed by precipitation with acetone, gave the crude *cis-3-aminocyclohexanecarboxylic acid* (4·8 g.). Sublimation at 270°/0·01 mm. and two more such precipitations gave microcrystals, m. p. 284° (decomp.) (Found: C, 58·6; H, 9·4; N, 9·7. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·2; N, 9·8%).

Derivatives of cis-3-*aminocyclohexanecarboxylic acid.* The benzoyl derivative prepared as described above had m. p. 166—167°, undepressed on admixture with that of the amino-acid obtained by hydrogenation. Treatment of this benzoyl derivative with *p*-bromophenacyl bromide gave *p-bromophenacyl cis-3-benzamidocyclohexanecarboxylate* (58%), which crystallised from acetone–ethanol as needles, m. p. 211—212° (Found: C, 59·6; H, 4·8. $C_{23}H_{22}O_4NBr$ requires C, 59·4; H, 5·0%). Treatment of the amino-acid with α-naphthyl *iso*cyanate gave the *α-naphthylcarbamoyl derivative*, which after many recrystallisations from ethanol was obtained as microcrystals, m. p. 207° (Found: N, 8·6. $C_{18}H_{20}O_2N_2$ requires N, 9·0%).

trans-3-*Aminocyclohexanecarboxylic Acid.*—Method (b) for the preparation of the *cis*-amino-acid when applied to *trans*-hexahydro*iso*phthalic acid gave trans-3-*aminocyclohexanecarboxylic acid* in similar yield. Purification by sublimation at 250°/0·01 mm., and precipitation with acetone from aqueous solution gave microcrystals, m. p. 290—291° (decomp.) (Found: C, 58·8; H, 9·3; N, 9·5%), depressed to 273—275° on admixture with the *cis*-epimer. Both amino-acids were completely insoluble in organic solvents—even methylformamide—nor did they give copper salts when their aqueous solutions were boiled with freshly prepared cupric hydroxide.

Derivatives of trans-3-*aminocyclohexanecarboxylic acid.* These were obtained by the foregoing methods and in similar yields. trans-3-*Benzamidocyclohexanecarboxylic acid* crystallised from chloroform–hexane as prisms, m. p. 195—196° (Found: C, 68·4; H, 6·8; N, 5·9%), depressed to 144—147° on admixture with the *cis*-epimer. The *p-bromophenacyl ester* crystallised from ethanol as needles, m. p. 182° (Found: C, 59·3; H, 4·7%), depressed to 170—173° on admixture with the *cis*-epimer. The *α-naphthylcarbamoyl derivative* was obtained from ethanol as microcrystals, m. p. 213—214° (Found: N, 9·3%), depressed to 200—202° on admixture with the *cis*-epimer.

Pyrolysis of cis-3-*Aminocyclohexanecarboxylic Acid.*—The *cis*-amino-acid (1 g.), in an N-shaped tube open at one end, was gently heated in a luminous flame until the volatile matter had been driven into the middle limb, where it partly solidified. The distillates from three such operations were taken up in hot ethanol. Removal of the solvent gave a residue (2·4 g.), which was extracted with hot benzene during 20 min., and the extract filtered from a very hygroscopic residue. Evaporation of the benzene gave a crystalline residue which was sublimed at 140°/0·1 mm. Several recrystallisations of the sublimate (1·2 g.) from hexane afforded the *lactam* as waxy prisms (0·75 g.), m. p. 198—199° (Found: C, 67·3; H, 8·8; N, 11·3%; *M*, 240. $C_7H_{11}ON$ requires C, 67·2; H, 8·9; N, 11·2%; *M*, 125). The same product (80 mg.) was obtained by pyrolysis of the *trans*-amino-acid (800 mg.).

The lactam (250 mg.) was hydrolysed by boiling aqueous barium hydroxide [10 ml. of 20% solution] during 2 hr. After quantitative removal of the barium as sulphate, the filtrate was evaporated, and the residue identified as *cis*-3-amino*cyclo*hexanecarboxylic acid by preparation of the benzoyl derivative (90 mg.), m. p. and mixed m. p. 166—167°.

6-*Aza*bicyclo[3 : 2 : 1]*octane.*—The lactam (250 mg.) in dry ether (25 ml.) was added to a suspension of lithium aluminium hydride (80 mg.) in ether (35 ml.), and the mixture heated under reflux for 4 hr. When cool, the excess of hydride was decomposed with water, followed by sulphuric acid (10%; 10 ml.), and the clear solutions were separated. Two more ethereal extracts of the aqueous layer were combined with the first and dried ($CaCl_2$), and the solvent was removed, leaving a residue (30 mg.) smelling strongly of the unreduced lactam.

The aqueous layer, which gave positive tests with both Mayer's and Wagner's reagents, was made sufficiently alkaline with sodium hydroxide to dissolve the precipitated alumina, and continuously extracted with ether. Removal of the solvent from the dried (K_2CO_3) extract left a crystalline residue of 6-aza*bicyclo*[3 : 2 : 1]octane, which had a strongly basic smell and fumed in air. The base was characterised as its *α-naphthylurethane*, which crystallised from benzene–hexane as prisms, m. p. 216—217° (Found: C, 77·0; H, 7·1; N, 9·7%; *M*, 301. $C_{18}H_{20}ON_2$ requires C, 77·1; H, 7·2; N, 10·0%; *M*, 280), and its *p-nitrobenzoyl derivative* which, after chromatography on alumina and elution with hexane–benzene (4 : 1) followed by

crystallisation from benzene–hexane, was obtained as needles, m. p. 128—129° (Found: C, 64·6; H, 6·2; N, 10·7%; *M*, 254. $C_{14}H_{16}O_3N_2$ requires C, 64·3; H, 6·6; N, 10·7%; *M*, 261).

Pyrolysis of cis-3-*Benzamidocyclohexanecarboxylic Acid.*—This acid (500 mg.) was pyrolysed in the manner described for the amino-acids. The partly solidified distillate was extracted from the tube with ethanol, the ethanol removed, and the residue extracted with three portions of boiling hexane. Evaporation of the hexane left an oil which was taken up in ether and extracted with aqueous sodium carbonate. The ethanol layer was dried ($MgSO_4$) and evaporated, leaving a residue which on crystallisation from hexane afforded the N-*benzoyl derivative* of the lactam as needles (40 mg.), m. p. 106—107° (Found: C, 73·9; H, 6·9; N, 6·3%; *M*, 236. $C_{14}H_{15}O_2N$ requires C, 73·3; H, 6·6; N, 6·1%; *M*, 229). Acidification of the aqueous layer, extraction with ether, and recrystallisation of the residue from chloroform–hexane yielded unchanged *cis*-3-benzamido*cyclo*hexanecarboxylic acid (20 mg.), m. p. and mixed m. p. 165—166°. Benzoic acid (120 mg.), m. p. and mixed m. p. 121°, was deposited on concentration of the mother-liquors.

We thank Professor A. Killen Macbeth for his interest. Microanalyses were carried out at the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

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The Halogenation of Phenolic Ethers and Anilides. Part XVII. An Investigation into the Additive Effects of Substituents in Benzyl Phenyl Ethers.*

By Brynmor Jones and Eileen N. Richardson.

[Reprint Order No. 6148.]

Kinetic studies of the nuclear chlorination of aromatic ethers of a wide variety of types have revealed that differences in rate arising from constitutional changes may be accounted for satisfactorily by variations in the energy of activation, with the substituents contributing in an additive manner.

In an attempt to delineate the extent of such behaviour, and to assess what departures from additivity are to be expected when polar groups are in close proximity to one another, rate constants have been determined for a series of benzyl phenyl ethers in which polar substituents occupy the *ortho*-positions of both the benzyl and phenyl groups.

The earlier kinetic studies in this series have shown the nuclear chlorination of aromatic ethers to be an eminently suitable reaction for the study of the influence of substituents on reactivity. In part, this is to be attributed to the method of chlorination developed by Orton and King (*J.*, 1911, **99**, 1360), whereby a known amount of chlorine can be liberated at will by the addition of hydrochloric acid to a chloramine in acetic acid, and, of equal importance, to the fact that the kinetics of the chlorination of ethers of wide variety are singularly free from complicating secondary reactions. From the accumulated rates of substitution, a remarkable degree of uniformity has been revealed in the effects of substituents on reactivity. Only in those ethers which contain one or more alkyl groups in the nucleus which undergoes substitution has any significant departure (of the order of 10—15%) from the strict constancy of velocity ratios been observed. As a result, it has been possible to analyse the data in terms of the equation $k = PZ \cdot e^{-E/RT}$, and to demonstrate that the differences in rate which arise from constitutional changes may be accounted for satisfactorily by variations in the energy of activation, changes in the entropy term P being almost negligible by comparison (cf. *J.*, 1942, 418, 676). When these relations had been established for ethers of the simple type *p*-RO·C_6H_4·X (where R and X were varied

* Part XVI, *J.*, 1954, 1775.

independently), series of ethers based on substituted cresols, xylenols, and hydroxybenzophenones, and on dihydroxydiphenyl sulphones and hydroxydiphenyls, were examined. In all these series the same pattern of behaviour was observed. Once the constancy of velocity ratios had been firmly established, however, for a wide range of ethers, it was of interest to try to delineate the extent of this behaviour by investigating compounds where some departure from additivity might be expected.

The present investigation constitutes a first attempt to reveal these departures. One condition which would be expected to militate against additivity is the presence in the molecule of two or more polar groups in close proximity to each other, for kinetic studies of a number of reactions have shown that the presence of *ortho*-substituents is generally conducive to anomalous results. The first compounds chosen were substituted benzyl phenyl ethers with polar substituents in the *ortho*-positions of both the benzyl and the phenyl group, since these afford opportunity for the operation and interplay of polar factors.

Tables 1—3 record the velocity constants for the series of 2-nitro-, 2-chloro-, 2-methyl-, 2 : 6-dichloro-, and 2 : 4 : 6-trimethyl-benzyl ethers, while in Tables 4 and 5 velocity ratios for *ortho*-substituted benzyl ethers of *ortho*-substituted phenols are compared with those for the same *ortho*-substituted benzyl ethers of phenols which have no *ortho*-substituents. Unfortunately, in some series, the benzyl ethers were liquids which proved extremely difficult to purify to the degree required in this study, and, in these series, the crystalline *p*-nitrobenzyl ethers were used as a standard of reference. In such cases, the ratio of the rate constants for the *o*-nitrobenzyl ether and the *p*-nitrobenzyl ether was multiplied by the value of k/k^* where k refers to *p*-bromophenyl 4-nitrobenzyl ether and k^* to *p*-bromophenyl benzyl ether.

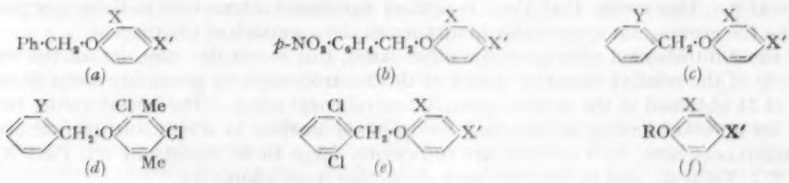

TABLE 1. *Benzyl and* p*-nitrobenzyl ethers. Velocity coefficients for the chlorination of ethers of the types* (*a*) *and* (*b*).

X	X′	k_{30}	X	X′	k_{30}
	Type (*a*)			*Type* (*b*)	
H	F	1·56	H	Cl	0·193
H	Cl	0·840	Me	Br	0·490
H	Br	0·805	Br	C_2H_5	0·976
Me	Cl	2·33	Br	Pr^n	0·739
Me	Br	2·16	Br	Bu^t	0·393
Br	Me	3·99	Br	CH_2Bu^t	0·333
Br	CH_2Bu^t	1·58			

TABLE 2. o-*Substituted benzyl ethers. Velocity coefficients for the chlorination of ethers of the types* (*c*) *and* (*d*).

Type (*c*)

X	X′	Y	k_{30}	X	X′	Y	k_{30}
H	F	NO_2	0·300	Br	Bu^t	NO_2	0·336
H	Cl	NO_2	0·178	H	Cl	Cl	0·335
Me	Cl	NO_2	0·362	Me	Br	Cl	0·897
Me	Br	NO_2	0·392	Br	Me	Cl	1·60
Br	Me	NO_2	0·802	H	Br	Me	1·10
Br	Et	NO_2	0·899	Me	Br	Me	3·29
Br	Pr^n	NO_2	0·650	Br	Me	Me	4·58
Br	CH_2Bu^t	NO_2	0·257				

Type (*d*)

Y	H	Me	Cl	NO_2
k_{30}	7·09	10·3	2·97	1·23

TABLE 3. *2 : 6-Dichlorobenzyl ethers. Velocity coefficients for the chlorination of ethers of the type (e).*

X	H	Me	Br
X′	Cl	Cl	Bu^t
k_{20}	0·275	0·859	0·697

TABLE 4. *Relative directive powers of the group* $O{\cdot}CH_2{\cdot}C_6H_4Y$ *in ethers of types (c) and (d). Values of* $100k/k^*$, *where k refers to group* $O{\cdot}CH_2{\cdot}C_6H_4Y$ *and k* to group* $O{\cdot}CH_2Ph$.

		Y						Y			
X	X′	H	*o*-Me	*o*-Cl	*o*-NO_2	X	X′	H	*o*-Me	*o*-Cl	*o*-NO_2
H	F	100	—	—	20·0	Br	Bu^t	100	—	—	18·0
H	Cl	100	—	39·9	21·0	Br	CH_2Bu^t	100	—	—	16·3
H	Br	100	137	—	—	Me	Br	100	142	41·6	16·8
Br	Me	100	116	40·3	20·1	Me	Cl	100	—	—	15·5
Br	Et	100	—	—	19·3	Dichloroxylyl ethers		100	137	41·8	17·4
Br	Pr^n	100	—	—	18·5						

Throughout, the solvent was 99% acetic acid (containing 1 ml. of water per 100 ml. of acetic acid), the concentrations of reagents were: ether 0·0225; chlorine 0·0075; hydrochloric acid 0·0375 mole/l.; and the velocity coefficients are expressed in l. mole^{-1} min.$^{-1}$ at 20°.

Discussion.—It is seen from the Tables that the 2-chlorobenzyl ethers in all series give the same value for the relative directive power—the maximum variation here is only from 39·9 to 41·8. This means that there is neither significant interaction in these compounds between the groups, nor appreciable hindrance to the approach of the reagent.

In the 2-nitrobenzyl ethers, on the other hand, this is not the case, for all the values (Table 4) of the relative directive power of the 2-nitrobenzyloxy group are lower than the value of 21 obtained in the *p*-chlorophenyl 2-nitrobenzyl ether. The lowest value, 15·5, is found for an ether having an *o*-methyl group in the nucleus in which substitution occurs. The differences here, 15·5 to 21·0, are sufficiently large to be significant (cf. Part X, *J.*, 1941, 272, Table 5), and to indicate some departure from additivity.

In the 2-methylbenzyl series, the lowest value, 115·7, is found in the 2-bromo-4-methylphenyl 2-methylbenzyl ether, which has a bromine atom in the *ortho*-position of the phenyl nucleus. The 2 : 6-dichlorobenzyl ether of *p*-chlorophenol has a directive power relative to that of the benzyl ether of 32·7, while that of the 2-chlorobenzyl ether of *p*-chlorophenol is 39·9. The deactivating effects of the two chlorine atoms are evidently not additive, for the influence of the second chlorine is small compared with that of the first.

TABLE 5. *Relative directive powers of the 2 : 6-dichlorobenzyloxy- and benzyloxy-group in ethers of type (f). Values of 100 k/k*, where k and k* refer to these two groups respectively.*

X	H	Me	Br
X′	Cl	Cl	Bu^t
100 k/k^*	32·7	36·8	37·2

In the two 2 : 6-dichlorobenzyl ethers which have *ortho*-substituents in the phenyl group—in one a methyl group, and in the other a bromine atom—the values of the relative directive power of the dichlorobenzyloxy-group, 36·8 and 37·2, are appreciably higher than the value 32·7 found for *p*-chlorophenyl 2 : 6-dichlorobenzyl ether.

The 2 : 4 : 6-trimethylbenzyl ethers are chlorinated so fast that it was impossible to obtain accurate figures for the velocity constants. The approximate values (350) found for *p*-chloro- and *p*-bromo-phenyl trimethylbenzyl ether are so much higher than the value of 4·83 for *p*-chlorophenyl 2 : 4-dimethylbenzyl ether that it must be concluded that rapid chlorination of the benzyl group occurs under the influence of the activating methyl groups, and that this masks the true reactivity of the phenyl group.

Experimental

Purification of Acetic Acid.—Acetic acid was purified by distillation from 2% of chromium trioxide (" AnalaR "), followed by redistillation from 0·2% of naphthalene-2-sulphonic acid and the theoretical amount of " AnalaR " acetic anhydride (Orton and Bradfield, *J.*, 1927, 983). Head and tail fractions were rejected, and the final distillate had m. p. 16·4°; this corresponds to 99·9% purity. The measurements were carried out in 99% acetic acid. This medium was stable to chlorine, and the difficulties experienced in Part XVI (*loc. cit.*) were not encountered.

Determination of Velocity Constants.—All measurements were made at 20° ± 0·02°. The procedure adopted was the same as in the earlier parts. The mean velocity constants obtained in different experiments did not differ by more than 3%.

The concentrations of ether and chlorine were always in the ratio 3 : 1. To ensure purity, solid ethers were crystallised at least four times, usually from benzene, ethanol, or acetic acid, and liquid ethers were fractionally distilled until a constant value was obtained for the velocity coefficient. This was found to be a more reliable criterion of purity than the more usual physical constants.

Materials.—Benzyl phenyl ethers were prepared by dissolving the phenol in a solution of one molecular proportion of sodium in absolute alcohol, adding one molecular proportion of the benzyl chloride in alcohol, and refluxing the mixture in a water-bath for 3—6 hr. The solid ethers were obtained on addition of water, after the bulk of the alcohol had been removed by distillation; the low-melting and liquid ethers were extracted with ether. The ether extract was washed free from phenol, and the benzyl ethers were crystallised or distilled.

2-Nitrobenzyl chloride was obtained from 2-nitrobenzyl alcohol by thionyl chloride in refluxing pyridine. It melted at 49·5° after crystallisation from acetic acid.

2-Methylbenzyl chloride, b. p. 192°/760 mm., was prepared in the same way from 2-methylbenzyl alcohol.

2 : 6-Dichlorobenzyl chloride was obtained by the chlorination of 2 : 6-dichlorotoluene, and the product, after distillation and crystallisation, had m. p. 35°.

3-Bromo-4-ethylphenol. Commerical *p*-hydroxyacetophenone was reduced (Clemmensen) to *p*-ethylphenol which was brominated in acetic acid with 1 mol. of bromine. The purified product had b. p. 110°/10 mm.

3-Bromo-4-n-propylphenol. Clemmensen reduction of *p*-hydroxypropiophenone gave *p*-*n*-propylphenol, which was brominated to the required product, b. p. 130°/20 mm.

3-Bromo-4-tert.-butylphenol. *p-tert.*-Butylphenol, in glacial acetic acid, was stirred during the dropwise addition of 1 mol. of bromine. The product obtained after fractionation had b. p. 120°/15 mm.

4-Bromo-o-cresol (OH = 1). *o*-Cresol was brominated in carbon tetrachloride at 0°. The product had m. p. 62—63°.

Those *ethers* which are new are listed.

Substituted benzyl phenyl ethers

Subst. in Ph	Subst. in CH_2Ph	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
p-Br	2-Me	62°	60·6	4·6	$C_{14}H_{13}OBr$	60·6	4·7
p-Cl	2 : 6-Cl_2	55	54·7	3·1	$C_{13}H_9OCl_3$	54·3	3·1
2 : 4-Cl_2	2-NO_2 *	126	52·4	3·1	$C_{12}H_8O_3NCl_3$	52·4	3·0
2 : 4-Cl_2	2 : 6-Cl_2 *	127	48·2	2·5	$C_{13}H_8OCl_4$	48·4	2·5
4-Cl-2-Me	—	40	72·0	5·4	$C_{14}H_{12}OCl$	72·3	5·6
4-Cl-2-Me	2-NO_2	110	60·6	4·4	$C_{14}H_{12}O_3NCl$	60·5	4·3
4-Br-2-Me	2-Me	28	62·1	5·3	$C_{15}H_{15}OBr$	61·9	5·2
4-Cl-2-Me	2 : 6-Cl_2	54	55·8	3·8	$C_{14}H_{11}OCl_3$	55·7	3·7
2-Br-4-Me	2-Me	48	62·0	5·3	$C_{15}H_{15}OBr$	61·9	5·2
2-Br-4-Bu^t	2 : 6-Cl_2	107	52·9	4·2	$C_{17}H_{17}OCl_2Br$	52·6	4·4
2 : 4-Cl_2-3 : 5-Me_2	2-Me	86	65·5	5·6	$C_{16}H_{16}OCl_2$	65·1	5·4
2 : 4-Cl_2-3 : 5-Me_2	2-NO_2	132	55·0	3·8	$C_{15}H_{13}O_3NCl_2$	55·2	4·0

* The solubility of these two ethers in 99% acetic acid at 20° was too low to enable any measurements to be made.

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A Synthesis of Methyl Homologues of Naphthols and Dihydroxynaphthalenes.

By Ng. Ph. Buu-Hoï and Denise Lavit.

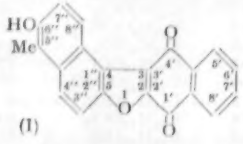
[Reprint Order No. 6334.]

A three-step method for the synthesis of methyl homologues of α- and β-naphthol and of dihydroxynaphthalenes consists of formylation of the corresponding methyl ether, reduction of the naphthaldehyde formed, and subsequent demethylation. Application of this method to α- and β-naphthol and to 2 : 6- and 2 : 7-dihydroxynaphthalene is reported.

Few convenient methods are known for introducing a methyl group into a β-naphthol. The methods due to Fries and Huebner [*Ber.*, 1906, **39**, 439; cf. Robinson and Weygand (*J.*, 1941, 386), Cornforth and Robinson (*J.*, 1942, 682), and Barclay, Burawoy, and Thompson (*J.*, 1944, 400)] cannot be extended to α-naphthols or dihydroxynaphthalenes and sometimes involve tedious separations. It has now been found that methyl groups can be readily introduced into α- or β-naphthol, or into dihydroxynaphthalenes, by formylation of the corresponding methyl ethers, Wolff–Kishner reduction (Huang-Minlon's technique, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) of the aldehyde, and demethylation with pyridine hydrochloride. This gives excellent overall yields of 1-methyl-2- and 4-methyl-1-naphthol and 1-methyl-2 : 6- and 1-methyl-2 : 7-dihydroxynaphthalene. The reaction sequence can be repeated, and from the last three substances were easily obtained 2 : 4-dimethyl-1-naphthol and 2 : 6-dihydroxy-1 : 5- and 2 : 7-dihydroxy-1 : 8-dimethylnaphthalene respectively.

Formylation of alkyl ethers of β-napthol is known to take place at position 1 (cf. Wood and Bost, *ibid.*, 1937, **59**, 1721; Buu-Hoï, Hoán, and Khenissi, *J.*, 1951, 2307), and this was now proved to hold for ethers of 2 : 6- and 2 : 7-dihydroxynaphthalene by identity of the aldehydes obtained with the methylation products of 2 : 6- and 2 : 7-dihydroxy-1-naphthaldehyde (Gattermann, *Annalen*, 1907, **357**, 313, 341; Morgan and Vining, *J.*, 1921, **119**, 177). Orientation of the formylation products of 1-methoxy- and 1-methoxy-4-methylnaphthalene was established by formation therefrom of the 4-methyl-1-naphthol (Lesser, *Annalen*, 1914, **402**, 1; Elbs and Christ, *J. prakt. Chem.*, 1923, **106**, 17) and 2 : 4-dimethyl-1-naphthol (Cornforth and Robinson, *loc. cit.*). In the formylation of 2 : 6-dimethoxynaphthalene, a small amount of 1 : 5-diformyl derivative was obtained, and this underwent Wolff–Kishner reduction to 2 : 6-dimethoxy-1 : 5-dimethylnaphthalene.

The dihydroxynaphthalenes prepared showed pronounced antioxidant properties, and are being tested for protective effects against lethal radiations (cf. Lacassagne, Duplan, and Buu-Hoï, *J. Nat. Cancer Inst.*, 1955, **15**, 915). With 2 : 3-dichloro-1 : 4-naphtha-



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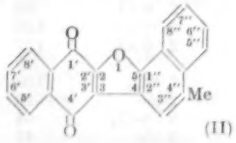

(II)

quinone (cf. Buu-Hoï, *J.*, 1952, 489) 1-methyl-2 : 6-dihydroxynaphthalene readily gave the quinone (I); the isomeric 1-methyl-2 : 7-dihydroxynaphthalene failed to react, probably on account of steric hindrance. 4-Methyl-1-naphthol gave, as was expected, the quinone (II) (cf. Buu-Hoï and Demerseman, *J.*, 1952, 4699).

In biological tests kindly performed by Dr. Chester Stock (Sloan-Kettering Institute for Cancer Research, New York), 4-methoxy-1-naphthaldehyde thiosemicarbazone inhibited growth of sarcoma 180 in mice, at a daily dose of 250 mg./kg. In tests for tuberculostatic properties *in vitro* (performed by Prof. Welsch, University of Liège), this substance was active against *Mycobacterium tuberculosis*, var. *hominis* (strain H37 Rv), only at a

concentration of $1 : 10^{-4}$, unlike anisaldehyde thiosemicarbazone, which is active at a concentration of $1 : 10^{-6}$.

Experimental

Preparation of 4-*Methoxy*-1-*naphthaldehyde*.—To a mixture of 1-methoxynaphthalene (90 g.) and dimethylformamide (47 g., or the equivalent amount of *N*-methylformanilide), phosphorus oxychloride (105 g.) was added portionwise, and the mixture heated for 3 hr. on a water-bath and then shaken with concentrated sodium acetate. The aldehyde was taken up in benzene, and the benzene solution washed with hydrochloric acid (6N), then with water, and dried (Na_2SO_4). The residue from evaporation of the solvent gave on fractionation *in vacuo* 4-methoxy-1-naphthaldehyde (86 g.), b. p. 205—206°/16 mm. Von Auwers and Frühling (*Annalen*, 1921, **422**, 198) gave b. p. 204—205°/15 mm. The *thiosemicarbazone* formed yellowish needles, m. p. 258°, from *n*-propanol (Found : C, 59·9; H, 5·1. $C_{13}H_{15}ON_3S$ requires C, 60·2; H, 5·0%); the 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone*, prepared from the foregoing compound with chloroacetic acid (cf. Buu-Hoï *et al.*, *J.*, 1952, 4590; 1954, 1975), formed pale yellow needles, m. p. 278°, from acetic acid (Found : C, 60·0; H, 4·5. $C_{15}H_{13}O_2N_3S$ requires C, 60·2; H, 4·3%); the isonicotinoylhydrazone formed yellowish prisms, m. p. 246°, from toluene (Found : C, 70·5; H, 4·9. $C_{18}H_{15}O_2N_3$ requires C, 70·8; H, 4·9%).

Preparation of 4-*Methyl*-1-*naphthol*.—A mixture of 4-methoxy-1-naphthaldehyde (83 g.), 95% hydrazine hydrate (40 g.), and diethylene glycol (500 c.c.) was heated at 100° for 5 min.; after cooling, potassium hydroxide (30 g.) was added, and the mixture was boiled until evolution of nitrogen ceased (45 min.). After addition of water, the product was taken up in benzene, and the benzene solution washed with dilute hydrochloric acid, then with water, and dried (Na_2SO_4), the solvent evaporated, and the residue fractionated *in vacuo*. 1-Methoxy-4-methylnaphthalene (69·5 g.) was a pale yellow oil, b. p. 154—155°/15 mm.; Kon and Ruzicka (*J.*, 1936, 187) gave b. p. 121°/0·8 mm. A mixture of this ether (34 g.) and pyridine hydrochloride (105 g.) was refluxed for 30 min. Water was added on cooling, and the product was taken up in chloroform and fractionated in a vacuum, giving 4-methyl-1-naphthol (20 g.), b. p. 165—167°/13 mm., which crystallised as silky, colourless needles, m. p. 85°, from ligroin; Lesser (*loc. cit.*) gave m. p. 84—85°. The picrate formed bright red needles, m. p. 179°, from ethanol.

4″-*Methyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-5 : 4)*furan*-1′ : 4′-*quinone* (II).—A solution of 4-methyl-1-naphthol (1 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (1·4 g.) in dry pyridine (15 c.c.) was refluxed for 10 min.; after cooling, ethanol was added, and the precipitated *quinone* recrystallised from nitrobenzene, giving orange needles, m. p. 275°, and giving with sulphuric acid the dark blue halochromy characteristic of brazanquinones derived from α-naphthols (Found : C, 80·5; H, 4·0. $C_{21}H_{12}O_3$ requires C, 80·8; H, 3·8%).

Preparation of 1-*Methyl*-2-*naphthol*.—2-Methoxy-1-naphthaldehyde was obtained in 90% yield as for the isomer, and was characterised by its *thiosemicarbazone*, shiny yellow leaflets, m. p. 166° (from ethanol) (Found : C, 60·1; H, 5·2%), and its isonicotinoylhydrazone, pale yellow leaflets, m. p. 209° (from ethanol) (Found : C, 70·6; H, 5·1%). Reduction gave 2-methoxy-1-methylnaphthalene (80% yield), m. p. 41°; Fries and Huebner (*loc. cit.*) gave m. p. 41—42°. Demethylation by pyridine hydrochloride afforded 1-methyl-2-naphthol (90% yield), m. p. 110—111° (lit., m. p. 111°).

1-*Methoxy*-4-*methyl*-2-*naphthaldehyde*.—A mixture of 1-methoxy-4-methylnaphthalene (69 g.), dimethylformamide (38 g., or the equivalent amount of *N*-methylformanilide), and phosphorus oxychloride (70 g.) was treated in the usual way, to yield 18 g. of 1-*methoxy*-4-*methyl*-2-*naphthaldehyde*, b. p. 185—186°/12 mm., crystallising as shiny, colourless prisms, m. p. 90°, from ethanol (Found : C, 78·0; H, 6·2. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%), giving a bright red solution in sulphuric acid. The *thiosemicarbazone* formed pale yellow needles, m. p. 266° (decomp. above 240° on prolonged heating), from acetic acid (Found : C, 61·9; H, 5·8. $C_{14}H_{15}ON_3S$ requires C, 61·5; H, 5·5%), and the 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone* formed silky yellow needles, m. p. 299—300°, from acetic acid (Found : C, 61·0; H, 5·1. $C_{16}H_{15}O_2N_3S$ requires C, 61·3; H, 4·8%).

1-*Methoxy*-2 : 4-*dimethylnaphthalene*.—The foregoing aldehyde (10 g.) gave, on reduction with hydrazine hydrate (5 g.) and potassium hydroxide (5 g.) in diethylene glycol (150 c.c.), 1-*methoxy*-2 : 4-*dimethylnaphthalene* (6 g.), b. p. 150—151°/12 mm., n_D^{22} 1·6055 (Found : C, 83·8; H, 7·5. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). Demethylation as above gave a 92% yield of 2 : 4-dimethyl-1-naphthol, m. p. 82—83° (from ligroin) [picrate (from ethanol), m. p. 144°]. Cornforth *et al.* (*loc. cit.*) gave m. p. 84—85° for the naphthol, and m. p. 143—144° for the picrate.

2 : 7-*Dimethoxy*-1-*naphthaldehyde*.—A mixture of 2 : 7-dimethoxynaphthalene (53 g.) (cf. Ullmann, *Annalen*, 1903, **327**, 104; Fischer and Kern, *J. prakt. Chem.*, 1916, **94**, 34), dimethylformamide (27·5 g.), phosphorus oxychloride (49 g.), and dry toluene (50 c.c.) was heated for 9 hr. on a water-bath, then for a further 30 min. with concentrated sodium acetate (when *N*-methylformanilide was used, heating was not necessary for hydrolysis of the imine). The product was taken up in benzene and treated in the usual way. 2 : 7-*Dimethoxy*-1-*naphthaldehyde* (50 g.), b. p. 230—231°/20 mm., crystallised as prisms, m. p. 98°, from ethanol (Found : C, 72·2; H, 5·5. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%). The same product was obtained by methylation of 2 : 7-dihydroxy-1-naphthaldehyde (Morgan and Vining, *loc. cit.*) with methyl iodide and potassium hydroxide in ethanol. The *thiosemicarbazone* formed yellowish needles, m. p. 183°, from acetic acid (Found : C, 58·0; H, 5·0. $C_{14}H_{15}O_2N_3S$ requires C, 58·1; H, 5·2%); the 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone* formed yellowish needles, m. p. 266°, from acetic acid (Found : C, 58·1; H, 4·3. $C_{16}H_{15}O_2N_3S$ requires C, 58·4; H, 4·6%).

2 : 7-*Dimethoxy*-1-*methylnaphthalene*.—Reduction of the foregoing aldehyde (37 g.) with hydrazine hydrate (16 g.) and potassium hydroxide (16 g.) in diethylene glycol (300 c.c.) yielded 2 : 7-*dimethoxy*-1-*methylnaphthalene* (31 g.), b. p. 178—179°/12 mm., needles, m. p. 58° (from ethanol) (Found : C, 77·0; H, 7·0. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%); the picrate formed red needles, m. p. 106°, from ethanol.

2 : 7-*Dihydroxy*-1-*methylnaphthalene*.—Demethylation of the foregoing methyl ether (3 g.) (15 minutes' boiling with 20 g. of pyridine hydrochloride) afforded 2 : 7-*dihydroxy*-1-*methylnaphthalene* (2·4 g.), colourless needles, m. p. 150° (from toluene) (Found : C, 75·6; H, 5·8. $C_{11}H_{10}O_2$ requires C, 75·9; H, 5·7%); the picrate formed brown-red needles, m. p. 169°, from methanol. This naphthol gave yellow solutions in aqueous sodium hydroxide, and did not react with 2 : 3-dichloro-1 : 4-naphthaquinone in pyridine; it readily autoxidised in solution.

2 : 7-*Dimethoxy*-8-*methyl*-1-*naphthaldehyde*.—A mixture of 2 : 7-dimethoxy-1-methylnaphthalene (27·5 g.), dimethylformamide (12·5 g.), phosphorus oxychloride (23·5 g.), and toluene (25 c.c.) was treated as for the lower homologue, to yield 26 g. of 2 : 7-*dimethoxy*-8-*methyl*-1-*naphthaldehyde*, b. p. 232—233°/14 mm., pale yellow needles, m. p. 96° (from ethanol) (Found : C, 72·9; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%).

2 : 7-*Dimethoxy*-1 : 8-*dimethylnaphthalene*.—Obtained by reducing the foregoing aldehyde (20 g.) with hydrazine hydrate (10 g.) and potassium hydroxide (10 g.) in diethylene glycol, this *ether* (14 g.), b. p. 199—200°/16 mm., formed colourless needles, m. p. 101°, from ethanol (Found : C, 77·7; H, 7·6. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%), and gave a picrate crystallising as brown-red needles, m. p. 118°, from ethanol.

2 : 7-*Dihydroxy*-1 : 8-*dimethylnaphthalene*.—Obtained from the foregoing methyl ether (5 g.) and pyridine hydrochloride (30 g.), 2 : 7-*dihydroxy*-1 : 8-*dimethylnaphthalene* (3·9 g.) formed colourless needles, m. p. 151—152°, from toluene, giving in aqueous sodium hydroxide a yellow solution (Found : C, 76·3; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

Formylation of 2 : 6-*Dimethoxynaphthalene*.—A mixture of 2 : 6-dimethoxynaphthalene (34·5 g.) (cf. Willstätter and Parnas, *Ber.*, 1907, **40**, 1406), dimethylformamide (17·5 g.), phosphorus oxychloride (32 g.), and toluene (25 c.c.), treated in the usual way, yielded : (*a*) a benzene-soluble portion, which gave on vacuum-distillation 2 : 6-*dimethoxy*-1-*naphthaldehyde* (32 g.), b. p. 223—225°/15 mm., yellowish prisms, m. p. 90° (from ethanol) (Found : C, 72·0; H, 5·6%) [*thiosemicarbazone*, greenish-yellow prisms, m. p. 215° (decomp. above 195° on prolonged heating), from ethanol (Found : C, 58·4; H, 5·3%); 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone*, yellow needles, m. p. 274°, from acetic acid (Found : C, 58·5; H, 4·5%); identical with the dimethylation product of 1-formyl-2 : 6-dihydroxynaphthalene with methyl iodide and potassium hydroxide in ethanol]; and (*b*) a benzene-insoluble portion (2 g.), consisting of 1 : 5-*diformyl*-2 : 6-*dimethoxynaphthalene*, bright yellow, sublimable needles, m. p. 273° (from acetic acid), giving a red halochromy in sulphuric acid (Found : C, 68·9; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·9; H, 4·9%).

2 : 6-*Dimethoxy*-1-*methylnaphthalene*.—Prepared from 1-formyl-2 : 6-dimethoxynaphthalene (27 g.), hydrazine hydrate (12 g.), and potassium hydroxide (12 g.) in diethylene glycol, this *ether* (22·1 g.), b. p. 185°/15 mm., formed colourless needles, m. p. 109°, from ethanol (Found : C, 77·1; H, 7·0%), giving a brown-red picrate (from benzene), m. p. 123°.

2 : 6-*Dihydroxy*-1-*methylnaphthalene*.—Prepared from the foregoing ether (3 g.) and pyridine hydrochloride (20 g.), this *compound* (2·1 g.) crystallised as sublimable needles, m. p. 206°, from toluene (Found : C, 76·3; H, 6·3%), which gave yellow solutions in aqueous sodium hydroxide. 6″-*Hydroxy*-5″-*methyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone*, prepared from this compound (1 g.), 2 : 3-dichloro-1 : 4-naphthaquinone, and pyridine (12 c.c.), formed brown-red

prisms, m. p. 233—234° (decomp.) (from nitrobenzene), giving with sulphuric acid the deep turquoise colour characteristic of brasanquinones derived from β-naphthols (Found: C, 76·6; H, 3·7. $C_{21}H_{12}O_4$ requires C, 76·8; H, 3·7%).

2 : 6-*Dimethoxy*-5-*methyl*-1-*naphthaldehyde*.—Prepared from 2 : 6-dimethoxy-1-methylnaphthalene (16 g.), dimethylformamide (7·5 g.). and phosphorus oxychloride (14 g.) in toluene (10 c.c.), this *aldehyde* (13·8 g.), b. p. 236—237°/15 mm., formed yellow prisms, m. p. 165°, from ethanol (Found: C, 73·1; H, 6·3%), giving a deep red colour with sulphuric acid; the *thiosemicarbazone* formed yellow leaflets, m. p. 240—241° (decomp. above 230° on prolonged heating), from acetic acid (Found: C, 59·0; H, 5·7. $C_{15}H_{17}O_2N_3S$ requires C, 59·4; H, 5·6%).

2 : 6-*Dimethoxy*-1 : 5-*dimethylnaphthalene*.—This compound (7·5 g.), obtained from the foregoing aldehyde (9·5 g.), hydrazine hydrate (4 g.), and potassium hydroxide (4 g.) in diethylene glycol (200 c.c.), crystallised as leaflets, m. p. 183°, b. p. 199—200°/17 mm., from ethanol (Found: C, 77·7; H, 7·4%), and gave a dark brown picrate, m. p. 133°, from benzene. The same substance was obtained on reduction of 1 : 5-diformyl-2 : 6-dimethoxynaphthalene.

2 : 6-*Dihydroxy*-1 : 5-*dimethylnaphthalene*.—This *substance* crystallised as sublimable needles, m. p. 298°, from acetic acid, becoming violet on exposure to the air and light (Found: C, 76·3; H, 6·2%), and soluble in aqueous alkalis; it autoxidised in solution much less readily than its 2 : 7-dihydroxy-isomer.

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The Determination of the Density of Liquid Bromine Pentafluoride.

By A. A. Banks and J. J. Maddock.

[Reprint Order No. 6257.]

The density of liquid bromine pentafluoride has been determined over the range −15° to +76° in sealed Pyrex glass dilatometers. There was no attack on the glass. The results are expressed in the equation $d_4^t = 2{\cdot}5509 - 3{\cdot}484 \times 10^{-3}t - 3{\cdot}45 \times 10^{-6}t^2$.

Ruff and Menzel (*Z. anorg. Chem.*, 1931, **202**, 49) gave an equation representing the variation of the density of liquid bromine pentafluoride with temperature. Unfortunately they did not report the range of temperature covered or the estimated accuracy of their results. There is no other recorded measurement of the density of the liquid.

The present determinations were carried out over the range −15° to +76° essentially as described by Banks and Rudge (*J.*, 1950, 191) for liquid chlorine trifluoride.

In calculating the results, all weighings were reduced to vacuum; the weight of bromine pentafluoride present as vapour was calculated on the assumption that the vapour obeys the ideal gas laws and the pressure from the equation * $\log p = 8{\cdot}0716 - 1627{\cdot}7/T$ (Ruff and Menzel, *loc. cit.*). The density values obtained were fitted to a curve of the type $d = a + bt + ct^2$ by the method of least squares, giving the equation *

$$d_4^t = 2{\cdot}5509 - 3{\cdot}484 \times 10^{-3}t - 3{\cdot}45 \times 10^{-6}t^2$$

The experimental results, together with the values calculated from the above equation, are shown in Table 1. Table 2 gives calculated values of the density of bromine pentafluoride at regular temperature intervals and at the boiling point [40·5° (Ruff and Menzel, *loc. cit.*)].

The plot of $d = 2{\cdot}550 - 3{\cdot}46 \times 10^{-3}t$ (Ruff and Menzel, *loc. cit.*) crosses the curve of the present equation at −20·00° and +13·04°. The divergence between the two equations is less than 0·1% from −30° to +30° and increases to 0·7% at 70°.

* In this paper T is the absolute temperature and t the temperature on the Centigrade scale.

TABLE 1.

Dilatometer No.	Temp.	*d* (obs.) (g./ml.)	*d* (calc.) (g./ml.)	$10^5(\Delta d)^2$ *	Dilatometer No.	Temp.	*d* (obs.) (g./ml.)	*d* (calc.) (g./ml.)	$10^5(\Delta d)^2$ *
6	−14·99°	2·6032	2·60235	72·2	3	40·80	2·4032	2·40301	3·6
5	− 4·29	2·5653	2·56579	24·0	2	42·94	2·3950	2·39494	0·4
1	+10·01	2·5150	2·51568	46·2	6	43·87	2·3916	2·39141	3·6
4	24·70	2·4621	2·46275	42·2	3	46·11	2·3832	2·38292	7·3
2	33·83	2·4290	2·42919	3·6	1	59·40	2·3319	2·33178	1·4
5	38·53	2·4120	2·41154	21·2	4	76·44	2·2639	2·26444	29·2

* $\Delta d = d$ (obs.) $- d$ (calc.). The R.M.S. deviation of the calculated values from the observed values is 0·00046.

TABLE 2.

Temp....	−20°	−10°	0	+10°	20°	30°	40°	40·5°	50°	60°	70°	80°
d (calc.)	2·6192	2·5854	2·5509	2·5157	2·4798	2·4433	2·4060	2·4041	2·3681	2·3294	2·2901	2·2501

EXPERIMENTAL

Bromine pentfluoride was prepared from the elements in the vapour phase at 300° (Found: Br, 45·5; F, 55·3. Calc. for BrF_5: Br, 45·7; F, 54·3%) and was freed from traces of hydrogen

FIG. 1.

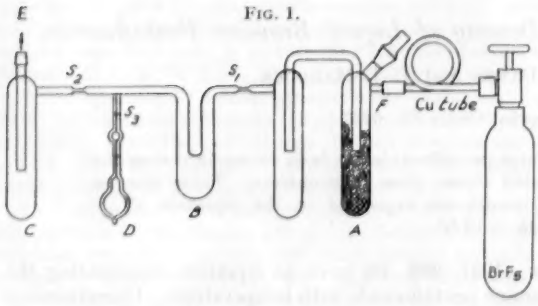
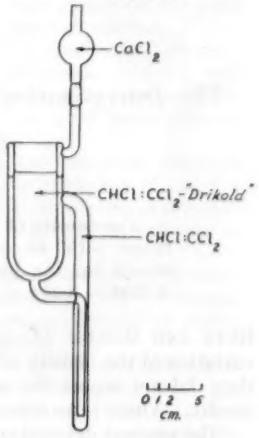


FIG. 2.



fluoride and bromine trifluoride by contact with sodium fluoride and further purified by distillation at reduced pressure.

A preliminary experiment designed to investigate the effect of bromine pentafluoride on glass was carried out to see whether there was any danger in sealing the liquid in glass dilatometers with very little free space. Weighed samples of Pyrex tube were sealed off *in vacuo* in ampoules containing sufficient bromine pentafluoride, purified by distillation through a tube packed with sodium fluoride pellets, to immerse half the specimen and were stored at room temperature for six days. The ampoules were then opened, the bromine pentafluoride was poured off and the samples were washed successively in wet carbon tetrachloride, dry carbon tetrachloride, and distilled water. They were reweighed after being dried at 140°. Samples of silica and of an experimental hydrogen fluoride-resistant glass (British Thomson-Houston Co. Ltd., Rugby) were also tested. All three types of glass showed weight losses not greater than 0·3 mg. for surface areas of 15—22 cm.^{2}.

The purification of this bromine pentafluoride was much less rigorous than that used during the dilatometer-filling operations and the method of destroying the film of bromine pentafluoride on the surface of the specimens probably led to a little attack by hydrogen fluoride. Even so, the overall effect on each of the samples was hardly measurable and it was considered

that more carefully purified bromine pentafluoride would be inert to Pyrex glass. The appearance of a trace of flocculent precipitate in the bromine pentafluoride in contact with the hydrogen fluoride-resistant glass sample indicated some slight reaction but there was no visible change in the contents of the remaining three ampoules.

Except for minor modifications, the technique used in the density determinations was essentially that described earlier (Banks and Rudge, *loc. cit.*) for the determination of the density of liquid chlorine trifluoride. Six dual-range dilatometers of 10 ml. capacity were used to obtain twelve results on six different samples of bromine pentafluoride.

The filling apparatus is shown in Fig. 1. Bromine pentafluoride vapour, led from a storage cylinder through a copper tube and Fyffe union *F*, was condensed *in vacuo* in trap *A* containing sodium fluoride pellets and cooled in solid carbon dioxide–trichloroethylene, dry air was admitted to the apparatus and, by removing the cooling bath from *A*, the solid pentafluoride was allowed to warm and melt. This procedure was repeated until sufficient bromine pentafluoride had been transferred. The liquid bromine pentafluoride, which at this stage had a very faint red colour, was allowed to remain in contact with the sodium fluoride for about half an hour and the apparatus was re-evacuated with trap *A* cooled in solid carbon dioxide. About 10% of the bromine pentafluoride was distilled into trap *C*, which was connected at *E* to the vacuum pump or dry air supply, cooled in liquid air until there was no trace of colour in the condensate. It is not known what impurity was responsible for this coloured fraction but in all cases the colour appeared only in the first fraction of the distillate. Trap *B* was then cooled in solid carbon dioxide–trichloroethylene, and bromine pentafluoride, in excess of that required to fill the dilatometer, was distilled into it. The dilatometer, *D*, and trap *B* were detached as a unit by sealing off *in vacuo* at the seals *S*1 and *S*2. The required amount of bromine pentfluoride was poured into the dilatometer and, after cooling both the dilatometer and the trap in liquid air, the dilatometer was sealed off at *S*3.

The Dewar flask with clear observation strips used as the thermostat for the work on chlorine trifluoride was used with minor modifications to give improved temperature control especially below room temperature. The thermosyphon cooling element shown in Fig. 2 was used, when required, to provide extra cooling and the thermostat temperature was controlled by electric heating as used for the higher temperatures. For reasons of safety, carbon tetrachloride was used rather than water as the bath liquid except during the measurement at 76° when trichloroethylene was used. To simplify the measurement of the position of the meniscus in the measurement capillaries, a calibration mark was etched at about the mid-point of each capillary and the temperature was adjusted to hold the meniscus steady for at least twenty min. on each of these marks in turn, the meniscus being observed through a telescope to eliminate parallax error. Temperatures were measured on a Beckmann thermometer graduated in 0·01° divisions which enabled minor fluctuations of temperature to be detected and controlled. The Beckmann thermometer was calibrated against mercury-in-glass thermometers calibrated by the N.P.L. to ±0·02°. For the two measurements below 0°, the Beckmann thermometer was calibrated against a Chromel–Alumel thermocouple calibrated by the N.P.L. to ±0·1°.

The dilatometers were emptied and calibrated with boiled-out distilled water by the method described previously except that for speed and simplicity the calibrations were carried out at 50° for the higher range of each dilatometer and 25° for the lower range. Two dilatometers were recalibrated to the lower mark at 75° and the results were used to determine the coefficient of expansion of the glass ($1{\cdot}0 \times 10^{-5}$, $1{\cdot}2 \times 10^{-5}$). The volume of each dilatometer at the experimental temperature was then calculated. Visual examination of the dry dilatometers, after calibration, revealed no evidence of etching.

From a consideration of the individual experimental errors involved, the expected measurement errors in the density values obtained are within ±0·0003 g./ml. for ten of the results and ±0·0006 g./ml. for the two results at temperatures below 0°.

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[*Received, March 22nd*, 1955.]

Studies in Mycological Chemistry. Part II. Proof of the Constitution of Flaviolin (2 : 5 : 7-Trihydroxy-1 : 4-naphthaquinone) by a Synthesis of Tri-O-methylflaviolin.*

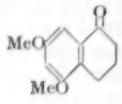
By J. E. Davies, F. E. King, and John C. Roberts.

[Reprint Order No. 6312.]

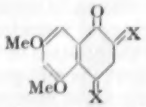
Syntheses of the isomeric 2 : 5 : 7- and 3 : 5 : 7-methoxy-1 : 4-naphthaquinones are described. It is shown that the 2 : 5 : 7-trimethyl ether is identical with tri-*O*-methylflaviolin, whence the constitution of flaviolin is established as the 2 : 5 : 7-trihydroxy-1 : 4-naphthaquinone.

Analytical and degradative methods have shown that flaviolin, a metabolic product of *Aspergillus citricus* (Wehmer) Mosseray, is 2(or 3) : 5 : 7-trihydroxy-1 : 4-naphthaquinone (Part I *). Further attempts to provide an unequivocal solution of the remaining structural problem have been directed towards the synthesis of the corresponding trimethyl ethers, and as already indicated (*Chem. and Ind.*, 1954, 1110) the results afford conclusive evidence that the structure of flaviolin is 2 : 5 : 7-trihydroxy-1 : 4-naphthaquinone.†

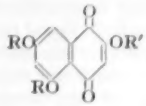
The usual methods for the hydroxylation of quinones, *viz.*, the hydrolysis and oxidation of products obtained therefrom by Thiele acetylation or the action of amines, are inapplicable in the present case since unsymmetrically *ar*-substituted 1 : 4-naphthaquinones give products of ambiguous constitution. An alternative route was therefore explored, based on the work of Pfeiffer and Hesse (*J. prakt. Chem.*, 1941, **158**, 315) and of Buu-Hoï and Cagniant (*Compt. rend.*, 1942, **214**, 87). This consists in the conversion of the appropriately substituted α-tetralone (*e.g.*, I) into a dianil (II), thus affording after hydrolysis a hydroxynaphthaquinone (III; R = Me, R′ = H) of unmistakable orientation.



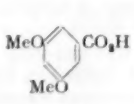
(I)



(II) X = *p*-N·C_6H_4·NMe_2



(III)



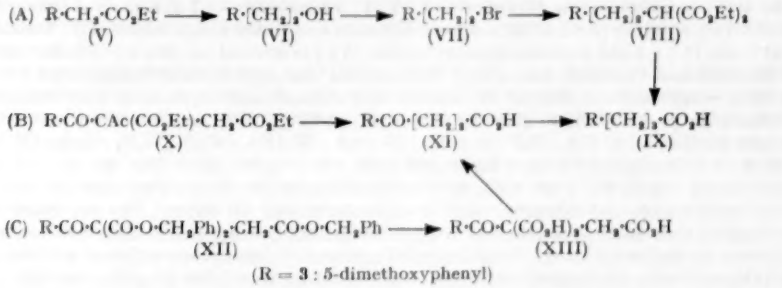
(IV)

2 : 5 : 7-Trimethoxy-1 : 4-naphthaquinone was synthesised in seven stages starting from resorcinol, which was converted by well-known methods into γ-(2 : 4-dimethoxyphenyl)butyric acid. Cyclisation of this acid proved to be extremely difficult and of the three different processes investigated the most efficient resulted in only 4—6% of 5 : 7-dimethoxytetral-1-one (I). Application of the Pfeiffer and Hesse reaction, followed by methylation, gave 2 : 5 : 7-trimethoxy-1 : 4-naphthaquinone (III; R = R′ = Me), m. p. 186—188°, unaltered on admixture with tri-*O*-methylflaviolin, m. p. 186—187°. The ultraviolet absorption spectrum of the synthetic compound also corresponded with that of tri-*O*-methylflaviolin.

3 : 5 : 7-Trimethoxy-1 : 4-naphthaquinone was synthesised in a twelve-stage process from benzoic acid, from which 3 : 5-dimethoxybenzoic acid was first prepared by standard procedures. The product (IV) was then homologated to the butyric acid (IX) by one of the annexed routes. Method A involved first the conversion of (IV) by the Arndt–Eistert reaction into the ester (V) and reduction of the latter by lithium aluminium hydride to the alcohol (VI). From the derived bromide (VII) the substituted malonic ester (VIII) was prepared and thence the butyric acid (IX). In method B the chloride of the acid (IV) was caused to react with ethyl sodioacetosuccinate [G. M. Robinson, *J.*, 1930, 745; cf. Thompson (*J.*, 1932, 2310) and Fieser and Dunn (*J. Amer. Chem. Soc.*, 1936, **58**, 572)], and the product (X) hydrolysed and decarboxylated to the keto-acid (XI). Reduction of the latter by the modified Wolff–Kishner method then gave (IX). Route C

* Part I, *J.*, 1953, 3302. † A preliminary account of an alternative synthesis of 2 : 5 : 7-trimethoxy-1 : 4-naphthaquinone has been published by Birch and Donovan (*Chem. and Ind.*, 1954, 1047).

follows the elegant homologation method of Bowman (*J.*, 1950, 325). Reaction between the chloride of the acid (IV) and benzyl ethane-1 : 1 : 2-tricarboxylate led to the product (XII) which was catalytically debenzylated to the acid (XIII). Decarboxylation of this acid gave the keto-acid (XI) which was reduced as before.


(A) R·CH₂·CO₂Et (V) → R·[CH₂]₂·OH (VI) → R·[CH₂]₂·Br (VII) → R·[CH₂]₂·CH(CO₂Et)₂ (VIII)
(B) R·CO·CAc(CO₂Et)·CH₂·CO₂Et (X) → R·CO·[CH₂]₂·CO₂H (XI) → R·[CH₂]₂·CO₂H (IX)
(C) R·CO·C(CO·O·CH₂Ph)₂·CH₂·CO·O·CH₂Ph (XII) → R·CO·C(CO₂H)₂·CH₂·CO₂H (XIII)
(R = 3 : 5-dimethoxyphenyl)

The last-mentioned process (C) proved the most expeditious and was used for the completion of the synthesis. Cyclisation of the substituted butyric acid (IX) led to 6 : 8-dimethoxytetral-1-one which was converted *via* the dianil and its hydrolysis product into 3 : 5 : 7-trimethoxy-1 : 4-naphthaquinone, m. p. 197—199°. The ultraviolet absorption spectrum of this compound differed from that of its isomer especially in the regions 240—300 and 325—400 mμ.

Experimental

Di-O-methylresorcinol.—This was prepared either from resorcinol, methyl sulphate, and aqueous sodium hydroxide (Ullmann, *Annalen*, 1903, **327**, 104) or, with more consistent results, by heating resorcinol (22 g.), anhydrous potassium carbonate (92·4 g.), methyl sulphate (61 g.), and dry acetone (350 c.c.) under reflux for 24 hr. and isolating the product, b. p. 216—218°, in the usual way (17·8 g., 66%).

β-(2 : 4-*Dimethoxybenzoyl*)*propionic Acid.*—Powdered aluminium chloride (75 g.) was added to a solution of the above ether (40·7 g.) and succinic anhydride (29·75 g.) in nitrobenzene (193 c.c.). After having been kept at room temperature for 2 days with occasional shaking, the mixture was poured into 12% hydrochloric acid (133 c.c.). By a procedure similar to that used for isolating β-(2 : 4-dimethoxybenzoyl)-α-methylpropionic acid (Schmid and Burger, *Helv. Chim. Acta*, 1952, **35**, 928) there was obtained β-(2 : 4-dimethoxybenzoyl)propionic acid (32·8 g., 67%), m. p. (after crystallisation from ethanol) 146—147°. Perkin and Robinson (*J.*, 1908, 506) give m. p. 146—148°. Yields varied from 45 to 85%.

γ-(2 : 4-*Dimethoxyphenyl*)*butyric Acid.*—This acid was prepared (i) by the modified Clemmensen reduction of the recrystallised keto-acid (yield 57%) using the method described for the corresponding α-methylbutyric acid (Schmid and Burger, *loc. cit.*) or (ii) by the modified Wolff–Kishner procedure (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487). β-(2 : 4-dimethoxybenzoyl)propionic acid (29·5 g. of unrecrystallised material), potassium hydroxide (32·5 g.), hydrazine hydrate (90%; 23·5 c.c.), and ethylene glycol (250 c.c.) were heated under reflux for 1½ hr. at 130° (bath) and then, after distillation of water, for 4 hr. at 200° (bath). The mixture was cooled, diluted with water, and acidified to Congo-red. The product was collected in ether, and the acid (10 g., 37%), b. p. 152—154°/0·1 mm., m. p. 45—47°, was isolated in the usual way. Mitter and De (*J. Indian Chem. Soc.*, 1939, **16**, 35) give m. p. 49°.

5 : 7-*Dimethoxytetral*-1-*one* (I).—The best results were obtained by working in batches. The foregoing acid (3 g.) was added, with stirring, to " polyphosphoric acid " [phosphoric oxide (12 g.) and " syrupy " phosphoric acid (10 c.c.)] at 165°. After 3 min. at this temperature the mixture was cooled to *ca.* 90° and triturated with water. The product (from nine such batches) was collected in ether, and the ethereal solution, after having been washed successively with sodium hydrogen carbonate solution, sodium carbonate solution, and water, was dried (Na_2SO_4) and the solvent was evaporated. Distillation of the residue gave 5 : 7-dimethoxytetral-1-one, b. p. 120—124°/0·1 mm. (1·75 g., 4·5%) which, even after crystallisation from light petroleum (b. p. 40—60°) (to give pale yellow prisms, m. p. 66—68°) was still slightly impure [Found :

C, 69·0; H, 6·6; OMe, 30·0. Calc. for $C_{16}H_8O(OMe)_2$: C, 69·9; H, 6·8; OMe, 30·0%]. Its 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–methanol in needles, m. p. 246° (decomp.) (Found : C, 55·5; H, 4·9; N, 14·6. $C_{18}H_{18}O_6N_4$ requires C, 56·0; H, 4·7; N, 14·5%).

Attempts to improve the efficiency of the cyclisation by using (i) anhydrous hydrofluoric acid (with the butyric acid) or (ii) stannic chloride (with the acyl chloride) were unsuccessful.

2 : 4-*Bis*-p-*dimethylaminophenylimino*-1 : 2 : 3 : 4-*tetrahydro*-5 : 7-*dimethoxy*-1-*oxonaphthalene* (II).—A 10% solution (2·8 c.c.) of sodium hydroxide was added to a solution of 5 : 7-dimethoxytetral-1-one (2·5 g.) and *p*-nitrosodimethylaniline (5 g.) in ethanol (*ca.* 50 c.c.) (Pfeiffer and Hesse, and Buu-Hoï and Cagniant, *locc. cit.*). The solution was kept at room temperature for 2 days. The dark violet solid was filtered off, washed with ethanol, and crystallised from benzene–light petroleum (b. p. 40—60°), to give the *dianil* (II) (2·65 g., 47%) as clusters of permanganate-coloured needles, m. p. 179—182° (decomp.) (Found : N, 11·6. $C_{28}H_{30}O_3N_4$ requires N, 11·9%).

2 : 5 : 7-*Trimethoxy*-1 : 4-*naphthaquinone* (III; R = R′ = Me).—The dianil (2·5 g.) was heated under reflux for 1 hr. with 30% sulphuric acid (60 c.c.). The mixture was cooled, diluted with water, and extracted with (i) chloroform and (ii) ether. The combined extracts were shaken with successive portions of aqueous sodium hydrogen carbonate solution until the latter was no longer coloured. The combined aqueous solutions were acidified and the product was collected with chloroform and ether. The solution was dried (Na_2SO_4) and the solvents were evaporated to give crude 2-hydroxy-5 : 7-dimethoxy-1 : 4-naphthaquinone (III; R = Me, R′ = H). This material (*ca.* 0·3 g.) was heated under reflux for ½ hr. with methanolic hydrogen chloride (3%; 4 c.c.) (cf. Fieser, *J. Amer. Chem. Soc.*, 1926, **48**, 2932). The solution was cooled, diluted with water, and extracted several times with benzene. The combined, dried (Na_2SO_4) benzene solutions were poured on to a column (10 × 1·3 cm.) of acid-washed alumina. Development of the chromatogram with (i) benzene, (ii) benzene containing 10% v/v of ether, and (iii) benzene containing 2% v/v of ethanol produced a broad, bright-yellow band which was eluted. Removal of the solvents *in vacuo* from the eluate and crystallisation of the residue from benzene–light letroleum (b. p. 40—60°) gave 2 : 5 : 7-trimethoxy-1 : 4-naphthaquinone (85 mg.) as golden-yellow prisms [Found : C, 62·8; H, 4·7; OMe, 34·7. Calc. for $C_{10}H_3O_3(OMe)_3$: C, 62·9; H, 4·9; OMe, 37·5%], m. p. 186—188°, unaltered by admixture with tri-*O*-methylflaviolin, m. p. 186—187°. Ultraviolet light absorption : Synthetic : $\lambda_{max.}$, 215, 260, 295, 412 mμ (log ε 4·49, 4·18, 4·03, 3·49 respectively). Natural : $\lambda_{max.}$, 214, 260, 296, 414 mμ (log ε 4·51, 4·20, 4·05, 3·42 respectively).

3 : 5-*Dimethoxybenzoic Acid*.—3 : 5-Dihydroxybenzoic acid (*Org. Synth.*, 1941, **21**, 27) was methylated by Mauthner's procedure (*J. prakt. Chem.*, 1913, **87**, 403).

3 : 5-*Dimethoxybenzoyl Chloride*.—The method used was essentially that of Mauthner (*loc. cit.*) but more consistent yields (64%) were obtained by using the modified proportions of phosphorus pentachloride (11·5 g.) to acid (10 g.). Very variable yields (0—90%) were obtained when attempts were made to prepare the acyl chloride by heating under reflux the acid (1 mol.) and thionyl chloride (1—2 mols.) for 1—1½ hr.

Ethyl 3 : 5-*Dimethoxyphenylacetate* (V).—A solution of 3 : 5-dimethoxybenzoyl chloride (30 g.) in ether (75 c.c.) was added dropwise, with stirring, to an ethereal solution (750 c.c.) of diazomethane (made from 52·5 g. of *N*-nitrosomethylurea). The solution was kept at room temperature for several hours and the solvent was then evaporated, to give an oil which later solidified (36 g.). A solution of this diazo-ketone in ethanol (540 c.c.) at 60° was treated with a slurry of silver oxide (from 3·75 g. of silver nitrate) in ethanol (162 c.c.). The mixture was then heated under reflux for 2 hr., boiled for a few minutes with charcoal, and filtered. The solvent was removed and the residue distilled, to give the ester (25 g., 75%), b. p. 128—132°/0·1 mm. Mühlemann (*Pharm. Acta Helv.*, 1951, **26**, 198) gives b. p. 144—146°/5 mm.

2-(3 : 5-*Dimethoxyphenyl*)*ethanol* (VI).—An ethereal solution of the foregoing ester (24 g.) was added, at such a rate to produce a steady reflux, to a rapidly stirred solution of lithium aluminium hydride (4 g.) in ether (275 c.c.). After the solution had been heated under reflux for 1 hr. and cooled, the excess of hydride was decomposed by the cautious addition of water (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197). The mixture was stirred into dilute sulphuric acid and the ethereal layer was separated, washed, and dried (Na_2SO_4). Evaporation of the solvent and distillation of the residue gave 2-(3 : 5-*dimethoxyphenyl*)*ethanol*, b. p. 126—130°/0·1 mm., 112—116°/0·01 mm., in yields of 40—70% (Found : C, 66·1; H, 7·7. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%).

2-(3 : 5-*Dimethoxyphenyl*)*ethyl Bromide* (VII).—Phosphorus tribromide (17·4 g.) was added dropwise (but without cooling) to the foregoing alcohol (17·6 g.), and the mixture was heated on the steam-bath for 1½ hr. and then poured on ice. The product was collected in ether, and

the ethereal solution was washed successively with aqueous sodium hydroxide solution (5%), water, 2N-hydrochloric acid, and water, and was then dried (Na_2SO_4). The solvent was evaporated and the residue distilled, without delay and at low pressure, to give slightly impure 2-(3 : 5-dimethoxyphenyl)ethyl bromide (9·52 g., 51%), b. p. 90—110°/0·05 mm. (Found : C, 49·9; H, 5·4; Br, 32·2. Calc. for $C_{10}H_{13}O_2Br$: C, 49·0; H, 5·3; Br, 32·5%). Barnes (*J. Amer. Chem. Soc.*, 1953, **75**, 3007) has experienced similar difficulties in attempting to obtain pure 2-(2 : 5-dimethoxyphenyl)ethyl bromide. These substances appear to lose hydrogen bromide with great ease.

β-(3 : 5-*Dimethoxybenzoyl*)*propionic Acid* (XI).—(i) *Route B.* A solution of 3 : 5-dimethoxybenzoyl chloride (37·1 g.) in ether (19 c.c.) was added slowly, with shaking, to an ethereal solution of ethyl sodioacetosuccinate [prepared from " powdered " sodium (4·5 g.), ethyl acetosuccinate (43 g.) (G. M. Robinson, *loc. cit.*), and dry ether (47 c.c.)]. After the mixture had been kept for two days at room temperature, the clear solution was decanted, washed successively with water and aqueous sodium carbonate solution, and then dried (Na_2SO_4). Evaporation of the solvent gave an oil [containing compound (X)] which was stirred for 2 days with a solution of potassium hydroxide (31·5 g.) in water (2000 c.c.). The resulting solution was acidified (concentrated hydrochloric acid) and the solid product filtered off. (A further quantity of product was obtained by ether-extraction of the filtrate.) Treatment of an ethanolic solution of this material with aqueous semicarbazide acetate, in the usual way, yielded a product which, after recrystallisation from ethanol, gave the *semicarbazone* of 2-(3 : 5-dimethoxybenzoyl)-propionic acid (5 g.) in slender needles, m. p. 156—158° (Found : C, 53·0; H, 5·8. $C_{13}H_{17}O_5N_3$ requires C, 52·9; H, 5·8%). [3 : 5-Dimethoxybenzoic acid (17 g.) was recovered from the mother-liquors.] This semicarbazone was heated under reflux for ½ hr. with 2N-hydrochloric acid, and the product was extracted with benzene. Evaporation of the solvent and crystallisation of the residue from benzene–light petroleum (b. p. 40—60°) gave β-(3 : 5-*dimethoxybenzoyl*)-*propionic acid* (2·6 g., 6% calc. on acyl chloride), m. p. 104—106° (Found : C, 60·2; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

(ii) *Route C.* A solution of 3 : 5-dimethoxybenzoyl chloride (13·3 g.) in dry benzene (100 c.c. ; " AnalaR ") was added, dropwise, with stirring, to a solution of benzyl sodioethane-1 : 1 : 2-tricarboxylate (16·9 g.) (Bowman, *loc. cit.*, p. 329) in benzene. The mixture was heated under reflux for ½ hr. and then poured into ice-water containing a small amount of dilute sulphuric acid. The organic layer was separated and the aqueous solution was extracted with benzene. The combined benzene solutions were dried (Na_2SO_4) and the solvent removed, first at 30—40°/*ca.* 15 mm., and secondly at 100°/0·5 mm,. to give a yellow-brown, viscous oil (XII). A solution of this material in ethanol (50 c.c.) and ethyl acetate (50 c.c.) was hydrogenated at atmospheric pressure using first palladium–charcoal (10% ; 0·5 g.) followed by palladium–strontium carbonate (10% ; 0·6 g.) as catalysts. A total of 3·66 l. of hydrogen was absorbed (maximum rate 1 l./hr.). The catalysts were removed and the solution was boiled under reflux for ½ hr., brisk evolution of carbon dioxide occurring. The solvents were evaporated and the residue was heated under reflux with 2N-sodium hydroxide for ½ hr. The resulting solution was cooled and acidified with 20N-sulphuric acid. The product, isolated by ether-extraction, was crystallised from very dilute acetic acid, to give β-(3 : 5-dimethoxybenzoyl)propionic acid (10 g., 63% from acyl chloride) in colourless plates, m. p. 90—96°. Recrystallisation from the same solvent gave material of m. p. 104—106° (semicarbazone, m. p. 156—158°).

γ-(3 : 5-*Dimethoxyphenyl*)*butyric Acid* (IX).—(i) *Route A.* A solution of 2-(3 : 5-dimethoxyphenyl)ethyl bromide (16 g.) in benzene (50 c.c.) was added slowly, and with stirring, to a benzene suspension of ethyl sodiomalonate [prepared from ethyl malonate (11 g.), " powdered " sodium (1·86 g.), and benzene (*ca.* 50 c.c.)]. After the mixture had been heated under reflux, with stirring, for 8 hr., the benzene was evaporated and the residue was mixed with water. The product, isolated by ether-extraction, was distilled. Collection of the distillate of b. p. <156°/0·1 mm. gave crude ethyl 2-(3 : 5-dimethoxyphenyl)ethylmalonate (VIII) (7·4 g., 35%). This ester was hydrolysed under reflux with 2N-sodium hydroxide for 2 hr. The solution was cooled and acidified and the 2-(3 : 5-dimethoxyphenyl)ethylmalonic acid (*ca.* 6 g.) was isolated by ether-extraction. This acid was decarboxylated at 180° for 1 hr., and the product was crystallised from *n*-hexane, or light petroleum (b. p. 40—60°), to give γ-(3 : 5-*dimethoxyphenyl*)-*butyric acid* (3·4 g., 23% from the bromide) in prisms, m. p. 56—58°. Recrystallisation from light petroleum (b. p. 40—60°) gave a specimen, m. p. 58—60° (Found : C, 64·0; H, 6·9. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2%).

(ii) *Route B or C.* β-(3 : 5-Dimethoxybenzoyl)propionic acid (XI) was reduced by the Huang-Minlon procedure as described above for the β-2 : 4-isomer. The reduced material,

when isolated in the usual way and crystallised from light petroleum (b. p. 40—60°), gave a product (yield 32%) which was identical with that described in method (i).

6 : 8-*Dimethoxytetral*-1-*one*.—(i) A mixture of the butyric acid (3 g.) and sulphuric acid (75%, 8 c.c.) was heated for 1 hr. on the steam-bath and then poured on ice. The ethereal solution of the product, having been washed first with dilute aqueous ammonia and then with water, was dried (Na_2SO_4) and the solvent was evaporated. (None of the original acid was recoverable from the alkaline washings.) The residue (*ca.* 1 g.) was extracted with successive quantities of boiling light petroleum (b. p. 60—80°). When the extracts were cooled, **6 : 8-*dimethoxytetral*-1-*one*** (0·82 g., 30%) separated in pale-yellow, slender prisms, m. p. 62—64° (Found : C, 70·2; H, 6·4. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). The **2 : 4-*dinitrophenylhydrazone*** crystallised from chloroform–methanol in needles, m. p. 214—216° (decomp.) (Found : C, 55·6; H, 4·9; N, 14·4. $C_{18}H_{18}O_6N_4$ requires C, 56·0; H, 4·7; N, 14·5%).

(ii) Ring-closure of the butyric acid by use of " polyphosphoric acid " at 145° (for method see above) gave a 24% yield of the tetralone.

(iii) Phosphorus pentachloride (3·8 g.) was added to a solution of the butyric acid (4 g.) in benzene (20 c.c.) at 0—10° and the solution was then warmed to 50° for a few minutes. A solution of stannic chloride (3·3 c.c.) in benzene (5·3 c.c.) was added, dropwise and with shaking, to the benzene solution of the acyl chloride, the temperature being kept below −5°. The mixture was then allowed to reach room temperature and, after having been warmed at 50° for 1 hr., was stirred into a mixture of ice and hydrochloric acid. The product was collected in ether, and the ethereal solution was washed successively with 2N-hydrochloric acid, saturated sodium hydrogen carbonate solution, potassium hydroxide solution (5%), and water. Evaporation of the solvent from the dried (Na_2SO_4) ethereal solution produced a residue which distilled at 170—190° (bath)/0·1 mm. to give the tetralone (0·26 g., 7%), m . p. 63—66°.

2 : 4-*Bis*-p-*dimethylaminophenylimino*-1 : 2 : 3 : 4-*tetrahydro*-6 : 8-*dimethoxy*-1-*oxonaphthalene*.—This substance was prepared in a similar manner to that which was used for its isomer (see above) except that a second crop of crude material was obtained by evaporation of the mother-liquor. The combined crops (1·8 g. from 1·08 g. of the tetralone, 77%) were washed with a little ethanol and dried. This ***dianil*** crystallised from benzene–light petroleum (b. p. 40—60°) in clusters of almost black needles, m. p. 206—208° (decomp.) (Found : C, 70·8; H, 6·1. $C_{28}H_{30}O_3N_4$ requires C, 71·5; H, 6·4%).

3 : 5 : 7-*Trimethoxy*-1 : 4-*naphthaquinone*.—The foregoing dianil (1·8 g.) was hydrolysed under reflux with 30% sulphuric acid (40 c.c.) and, by a method similar to that used for isolating the compound (III; R = Me, R′ = H), there was obtained crude 3-hydroxy-5 : 7-dimethoxy-1 : 4-naphthaquinone. This material (*ca.* 0·15 g.) was methylated with methanolic hydrogen chloride, and the product collected in benzene. Chromatography on a column of acid-washed alumina gave a broad, yellow band which was readily eluted with benzene containing 10% v/v of ether. Evaporation of the solvents from the eluate and crystallisation of the residue from benzene–light petroleum (b. p. 40—60°) gave **3 : 5 : 7-*trimethoxy*-1 : 4-*naphthaquinone*** (60 mg.) in yellow, slender prisms, m. p. 197—199° (altered to *ca.* 165° on admixture with its isomer) [Found : C, 62·8; H, 5·1; OMe, 37·6. $C_{10}H_3O_2(OMe)_3$ requires C, 62·9; H, 4·9; OMe, 37·5%]. Ultraviolet light absorption : $\lambda_{max.}$ 213, 267, 293, 402 mμ (log ε 4·54, 4·18, 4·23, 3·56 respectively).

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The Preparation of Halogen-bridged Complexes of Platinum(II).

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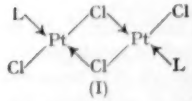
General methods for the preparation of binuclear platinous chloride complexes of the type $L_2Pt_2Cl_4$ (I) have been developed, and their application to the preparation of complexes with different uncharged ligands, L, has been critically examined. Compounds containing as the ligands, L, olefins, amines, tertiary organic phosphines, arsines, and stibines, and dialkyl sulphides, selenides, and tellurides are described.

During an investigation of inductive and mesomeric effects in platinous complexes it became necessary to prepare a wide variety of chlorine-bridged platinous complexes of type (I) (L = any uncharged ligand), and we now report the development of existing and new methods of doing this.



(I)

Although there was considerable development of methods of preparing the halogen-bridged complexes of many metals, particularly palladium, during the 1930's (see Mann, *Ann. Reports*, 1938, **35**, 148), surprisingly few halogen-bridged platinous complexes were known before 1951, and no obviously general methods for their preparation. We then published an account of two general methods which we had developed for the preparation of halogen-bridged complexes having trialkyl-phosphines, -arsines, and -stibines as the ligand, L (Chatt, *J.*, 1951, 652). We have now developed these and other methods to give bridged complexes having as the ligands, L, substances containing nitrogen, sulphur, selenium, and tellurium as donor atoms. It seems useful therefore to summarise the methods at present available.

(1) *Reaction of Finely Powdered* $PtCl_2$ *with a Melt of* cis- *and/or* trans-L_2PtCl_2 (Chatt, *loc. cit.*): $L_2PtCl_2 + PtCl_2 \longrightarrow L_2Pt_2Cl_4$.—This is one of the most useful general methods, but it is limited to preparations in which L_2PtCl_2 melts without decomposition (other than isomerisation) and the product has sufficient thermal stability to withstand the temperatures used. It is best suited to preparing the tri-*n*-propyl and higher homologues of the series $(PR_3)_2Pt_2Cl_4$, $(AsR_3)_2Pt_2Cl_4$, and $(R_2S)_2Pt_2Cl_4$, but it becomes increasingly difficult to apply as one descends the homologous series because the higher melting points of the simple complexes, L_2PtCl_2, and therefore higher reaction temperatures, lead to greater decomposition of the products. The corresponding bromo-complexes can be prepared by a similar reaction. Our attempts to prepare trialkylstibine, dialkyl selenide, dialkyl telluride, and amine-bridged complexes by this method yielded mainly black decomposition products.

(2) *Reaction of* cis-L_2PtX_2 *with* M_2PtCl_4 *in Solution* (X = univalent acid radical, M = alkali metal): $L_2PtX_2 + M_2PtCl_4 \longrightarrow L_2Pt_2Cl_4 + 2MX$.—This method was used to prepare $(Et_2S)_2Pt_2Cl_4$ and $(Pr_2S)_2Pt_2Cl_4$ towards the end of the last century (Blomstrand, *J. prakt. Chem.*, 1888, **38**, 352; Klason, *Ber.*, 1895, **28**, 1493; Rudelius, *Acta Univers. Lund*, 1885—1886, **22**, Part 2, Paper 4) but these early investigators used chloro-complexes (X = Cl) which they treated with warm aqueous K_2PtCl_4. Since the mixture was not homogeneous the reactions were very slow. In the case of the lower alkyl members of the series homogeneity in aqueous solution can be obtained by employing the complexes of oxygen-acids which dissolve in water probably as aquo-ions, *e.g.*, $[(Et_2S)_2Pt(H_2O)_2]^{++}$. In this way Petren (Diss., Lund, 1898, p. 38) prepared $(Et_2Se)_2Pt_2Cl_4$ from *cis*-$(Et_2Se)_2Pt(NO_3)_2$ and K_2PtCl_4 in cold aqueous solution, and Jensen (*Z. anorg. Chem.*, 1935, **225**, 115) obtained $(Et_2S)_2Pt_2Cl_4$ and $(Pr_2S)_2Pt_2Cl_4$ similarly from the corresponding sulphates. This method has the disadvantage that the simple complexes of oxygen-acids cannot be prepared by direct methods but must be prepared from the chloro-complexes. We have therefore developed a further modification employing chloro-complexes of *cis*-configuration in ethanolic Na_2PtCl_4 solution. Jensen's and this modification have their own fields of application.

(*a*) When *cis*-$[L_2PtCl_2]$ is difficult to obtain, as in the dialkylselenide series of complexes, the *trans*-isomer is converted into an aqueous solution of the sulphate by the reaction

$$trans\text{-}[L_2PtCl_2] + Ag_2SO_4 \longrightarrow L_2PtSO_4.aq. + 2AgCl$$

with the reactants in warm aqueous suspension. This solution on treatment with aqueous K_2PtCl_4 then yields the bridged complexes.

(*b*) When *cis*-$[L_2PtCl_2]$ is readily available, it is treated in homogeneous solution with absolute ethanolic Na_2PtCl_4 at a suitable temperature until reaction is complete (about 30° for 40 hr. in the case of dialkyl sulphide complexes, and 20° for 16 hr. in the case of dialkyl telluride complexes). Since the simple dialkyl telluride complexes isomerise spontaneously, the bridged compounds may be prepared directly by adding 1 mol. of R_2Te to 1 mol. of Na_2PtCl_4 in ethanol, and keeping the solution for 16 hr. Trialkylstibine complexes are not obtained by this method, and dimethyl sulphide yields insoluble $(Me_2S)_3Pt_2Cl_4$. *trans*-$[(R_2S)_2PtCl_2]$ does react with ethanolic Na_2PtCl_4, but much too slowly to provide a preparative method. An ethanolic solution of *trans*-$[(R_2Se)_2PtCl_2]$ blackens on addition of ethanolic Na_2PtCl_4.

(3) *Thermal Decomposition of Olefin Complexes*, $[un,L,PtCl_2]$ (un = olefin, *e.g.*, C_2H_4 or C_3H_6): $2[un,LPtCl_2] \longrightarrow L_2Pt_2Cl_4 + 2un$.—This is probably the method of most general applicability, but because olefin complexes are not convenient raw materials it is reserved for use when the first two methods have failed. It is the best method of obtaining the insoluble or almost insoluble bridged complexes of the lowest members of a homologous series, and the only method by which we have obtained trialkylstibine and amine-bridged complexes. Two procedures were employed, depending on the nature of the ligand, L.

(*a*) When L is a ligand of moderate to high *trans*-effect, the species *trans*-$[un,LPtCl_2]$ decomposes spontaneously at a low or moderate temperature. In such a case it is sufficient to treat an acetone or dichloromethane solution of the bridged olefin complex, $un_2Pt_2Cl_4$, with the theoretical quantity of the free ligand at −75°, and allow the mixture to warm until decomposition occurs. When L contains phosphorus, arsenic, or antimony as donor atom decomposition occurs at about or below room temperature, but if it contains sulphur as donor, 50—70° is necessary for a reasonable rate of decomposition. Anderson's method (*J.*, 1936, 1042) of replacing ethylene from $(C_2H_4)_2Pt_2Cl_4$ by a less volatile olefin is a special application of this procedure. Amines (am) usually give indefinite oily products by this procedure although the remarkably stable *cis*-$[am,un,PtCl_2]$ is sometimes obtained.

(*b*) To obtain amine-bridged complexes it is best to prepare *trans*-$[am,un,PtCl_2]$ by the careful neutralisation with sodium hydroxide of a 3% hydrochloric acid solution of the amine hydrochloride containing $K[un,PtCl_3]$, and allow it to decompose spontaneously at room temperature in a solvent in which the product, $am_2Pt_2Cl_4$, is insoluble. Light petroleum is often most satisfactory but the decomposition is slow and may require a week to several months depending on the amine and olefin present in the complex. Warming the solution speeds the reaction but causes side reactions and further decomposition of the product so that a complex mixture is obtained including, as minor product, the bridged complex. The propylene complexes decompose more quickly than the ethylene complexes and it may be that this preparation could be improved by the use of some higher olefin such as pentene.

(4) *Decomposition of the Acids* $H[LPtCl_3]$: $2H[LPtCl_3] \longrightarrow L_2Pt_2Cl_4 + 2HCl$.—These acids decompose spontaneously when their solutions are taken to dryness. However, the method is severely limited because salts containing ions of the type $[LPtCl_3]^-$ are not very common. It is the only certain method of obtaining $(C_2H_4)_2Pt_2Cl_4$ and $(C_3H_6)_2Pt_2Cl_4$ in good yields (Chatt and Duncanson, *J.*, 1953, 2939) and is doubtless the final stage in the complex series of reactions between Na_2PtCl_6 and ethanol which constitutes Anderson's preparation of $(C_2H_4)_2Pt_2Cl_4$ (*J.*, 1934, 971). The method has also been used to yield $(NH_3)_2Pt_2Cl_4$ (Klason, *J. prakt. Chem.*, 1903, **67**, 1), $(CO)_2Pt_2Br_4$, and $(CO)_2Pt_2I_4$ (Hieber, Ries, and Bader, *Z. anorg. Chem.*, 1930, **190**, 215).

(5) *Reaction of a Weakly Co-ordinating Reducing Ligand with* $PtCl_4$ *or* $PtBr_4$ *in Acetic Acid or Benzene Suspension*: $4L + 2PtCl_4 \longrightarrow L_2Pt_2Cl_4 + 2LCl_2$.—This occurs rapidly at 100° but has so far been used only to prepare olefin complexes (Kharasch and Ashford,

J. Amer. Chem. Soc., 1936, **58**, 1733). It is not convenient when the olefin is gaseous. In our hands it has not given good yields and we prefer method (3) for the preparation of higher olefin complexes. With dipentene the two methods yield different isomeric, but not bridged products (Chatt and Wilkins, *J.*, 1952, 2622).

(6) *Miscellaneous Special Methods.*—The first halogen-bridged platinous complexes to be prepared were not typical and the methods of preparation were incapable of general application. These, with their dates of discovery and most recent detailed references are :

(*a*) $2CO + 2Pt + 2Cl_2 \xrightarrow{240°} (CO)_2Pt_2Cl_4$ (1868; Hieber, Ries, and Bader, *loc. cit.*).

(*b*) $2PCl_5 + 2Pt \xrightarrow{>200°} (PCl_3)_2Pt_2Cl_4$ (1872; Arbuzov and Zoroastrova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1952, 818; Rosenheim and Levy, *Z. anorg. Chem.*, 1905, **43**, 34).

(*c*) $2PBr_5 + 2Pt \xrightarrow{200°} (PBr_3)_2Pt_2Br_4$ (1905; Rosenheim and Levy, *loc. cit.*).

(*d*) $(PCl_3)_2Pt_2Cl_4 + 6ROH \xrightarrow{<20°} [P(OR)_3]_2Pt_2Cl_4$ [1872; see refs. to (*b*)].

(*e*) $2PF_3 + 2PtCl_2 \xrightarrow{>200°} (PF_3)_2Pt_2Cl_4$ (1950; Chatt and Williams, *J.*, 1951, 3061).

General Properties of the Halogen-bridged Complexes.—It is interesting to compare the general properties of the chloride-bridged complexes having as ligands the organic derivatives of nitrogen, phosphorus, arsenic, antimony, sulphur, selenium, and tellurium. The

Melting points, colours, and methods of preparation of bridged platinous complexes, $L_2Pt_2Cl_4$.

Ligand L	Method of preparation	M. p.	Colour
Piperidine *	3*b*	182—192° (decomp.)	Yellowish-orange
4-*n*-Pentylpyridine *	3*b*	121—122	,,
4-*n*-Nonylpyridine *	3*b*	132—133·5	,,
p-Toluidine *	3*b*	180—190 (decomp.)	Reddish-orange
PMe_3 *	3*a*	217—220 (decomp.)	Yellowish-orange
PEt_3	1	223—224	,,
PPr^n_3	1(3*a*)	182—183	,,
PBu^n_3 *	1	143—144	,,
PAm^n_3 *	1	121—122	,,
$PHex^n_3$ *	1	120—120·5	,,
$PPhBu^n_2$ *	1	167—171 (decomp.)	,,
$AsEt_3$ *	1	208—209 (decomp.)	Orange
$AsPr^n_3$	1	194—197 (decomp.)	,,
$AsBu^n_3$ *	1	126—127	,,
$SbMe_3$ *	3*a*	150—170 (decomp.)	Reddish-orange
$SbEt_3$ *	3*a*	130—135 (decomp.)	,,
$SbPr^n_3$	3*a*	133—134 (decomp.)	,,
Me_2S *	3*a*	200—220 (decomp.)	Mustard-yellow
Et_2S	2*b*(1)	213—230 (decomp.)	Bright yellow
Pr^n_2S	1(2*a*)	194—197 (decomp.)	,,
Bu^n_2S *	1	188—198 (decomp.)	,,
Oct^n_2S *	2*b*	148—166 (decomp.)	,,
Et_2Se	2*a*	146—147 (decomp.)	Brownish-orange
Pr^n_2Se *	2*a*(1)	76·5—77·5 (decomp.)	,,
Et_2Te *	2*b*	142 (decomp.)	Brownish-orange
Pr^n_2Te *	2*b*(1)	120—131 (decomp.)	,,

* Ligands whose bridged $PtCl_2$ compounds were previously unknown are marked *.

colours, melting or decomposition temperatures, and methods of preparation are listed in the Table.

The trialkyl-phosphine, -arsine, and -stibine chloride-bridged complexes are all beautifully crystalline substances soluble in many organic solvents such as benzene, acetone, and chloroform. Solubility increases rapidly as the homologous series is ascended from the sparingly soluble methyl to conveniently soluble propyl derivatives, then more slowly as the homologous series is ascended further. Solubility also increases on ascending the eutropic series from the phosphine to stibine complexes. Stability falls rapidly in the same series: the phosphine complexes are very stable; the arsine complexes decompose very slowly in boiling ethanolic solution and the stibine complexes decompose spontaneously in

any warm solvent. The stabilities of the stibine complexes also decrease rapidly on ascending the homologous series from the trimethyl to tri-*n*-propyl complex. This appears to be a general property of stibine complexes; it is most marked in the series $(R_3Sb)_2PdCl_2$ and to a lesser extent in the more stable series $(R_3Sb)_2PtCl_2$ (Chatt and Wilkins, *J.*, **1953**, 70). The amine complexes lie between the arsine and stibine complexes in general stability and crystallise well from low-boiling solvents provided the operation is carried out rapidly.

By contrast, the bridged complexes containing sixth-group donor atoms do not give a series of complexes having well-graded properties; this is obvious even from their colours (see table). The dialkyl sulphide series of complexes is the most insoluble we have prepared. The dimethyl and diethyl sulphide complexes are practically insoluble in all solvents tried, but the dipropyl sulphide complex is slightly soluble in some boiling solvents such as chloroform and ethyl methyl ketone. Solubility increases as the homologous series is ascended. The diethyl selenide and telluride complexes, which resemble each other closely, are moderately soluble in organic solvents, those containing selenium being most soluble. In stability the sulphide are comparable with the phosphine complexes; the telluride complexes are slightly more stable than the trialkylstibine complexes, yet the selenide complexes are the least stable of any bridged series of complexes that we have prepared. Purification of the selenide complexes is difficult, and analytical purity often deteriorates on attempted recrystallisation. The bridged structure appears to be confirmed by the molecular weight of $(Et_2Se)_2Pt_2Cl_4$ (Petren, *loc. cit.*) and such bridge-splitting reactions as:

$$(Et_2Se)_2Pt_2Cl_4 + 2 \text{ piperidine} \longrightarrow 2[Et_2Se, \text{piperidine}, PtCl_2]$$

Our general experience in handling the chloride-bridged compounds indicates that the stabilities fall in the sequence: $PR_3 \sim R_2S > AsR_3 >$ amine $> R_2Te > SbR_3 > R_2Se$. In placing amines in this series it must be emphasised that the amines studied were not trialkylamines but primary, secondary, and heterocyclic amines which are known to yield stable platinous complexes; they are not strictly comparable with the organic derivatives of the other donor atoms. It seems unlikely that bridged complexes of the type $(NR_3)_2Pt_2Cl_4$ will be obtained, but if they were obtained they would probably be less stable than $(R_2Se)_2Pt_2Cl_4$ (see Chatt and Wilkins, *J.*, 1952, 4300).

Since complex salts containing two complex ions have sometimes been formulated as covalent bridged complexes (see Foss and Gibson, *J.*, **1949**, 3063; Nyholm, *J.*, **1951**, 1767), the conductivities of all the above types of bridged complexes were measured in nitrobenzene solution, and their covalent character was confirmed.

Only two bromide- and one iodide-bridged complexes were prepared: the former by the fusion method (1) using L_2PtBr_2, and the latter by reaction of sodium iodide (4 mols.) with the chloride-bridged complex in acetone solution (Chatt, *loc. cit.*).

Experimental

(Microanalyses marked * are by Messrs. Weiser and Ritter of Basle; the remainder are by Messrs. Brown and Olney of these laboratories.)

Most of the halogen-bridged compounds described in this section are new; those which are not new have been prepared by improved methods. The simple complexes of type L_2PtCl_2, required as starting materials for many of the preparations below, were prepared by shaking 2 equiv. of the ligand, L, with aqueous K_2PtCl_4 (Jensen, *loc. cit.*; *Z. anorg. Chem.*, **1936**, **229**, 250). This reaction is slow, especially for the preparation of the higher alkyl derivatives, and so in later preparations it was accelerated by treating an ethanolic solution of Na_2PtCl_4 at room temperature, or a dilute acetic acid solution of K_2PtCl_4 at boiling temperature, with the ligand. The bromides, L_2PtBr_2, were obtained by adding potassium bromide (100% excess) to the aqueous K_2PtCl_4 solution then proceeding as in the preparation of chlorides.

Method 1. In general application a thoroughly dried, coarsely powdered mixture of the crude isomers of L_2PtCl_2 or L_2PtBr_2 is intimately mixed with finely powdered $PtCl_2$ or $PtBr_2$ (1 mol.) respectively. The mixture is then warmed in a boiling tube until it is sufficiently fluid to be stirred with a thermometer. It is stirred continuously, and the temperature maintained until the melt becomes pasty owing to separation of the higher-melting bridged product. When the reaction appears complete (about 15 min.) the melt is allowed to cool, and the solid product extracted with a suitable boiling solvent (usually acetone). The solution is then treated with

charcoal to remove traces of colloidal platinum, and filtered; the bridged compound separates as the filtrate cools. The following compounds have been prepared by this method. The temperature and time of reaction, extraction solvent, solvent used for recrystallisation (if different), and yield of pure products are given in parentheses.

Bistri-n-*butylphosphinedichloro-μμ′-dichlorodiplatinum* (130°, 15 min., acetone, 55·7%) (Found: C, 30·7; H, 5·8; *M*, ebullioscopic in 1·5% benzene solution, 956. $C_{24}H_{54}Cl_4P_2Pt_2$ requires C, 30·8; H, 5·8%; *M*, 937); the *tri*-n-*pentyl* analogue (110—120°; 15 min., acetone, methanol, 49%) (Found: C, 35·45; H, 6·7. $C_{30}H_{66}Cl_4P_2Pt_2$ requires C, 35·3; H, 6·5%); the *tri*-n-*hexyl* analogue (100°, 30 min. but no solidification of the melt, ethyl methyl ketone, methanol, 12%) (Found: C, 38·8; H, 7·0. $C_{36}H_{78}Cl_4P_2Pt_2$ requires C, 39·1; H, 7·1%); the (*di*-n-*butyl*)*phenyl* analogue (144°, 15 min., ethyl methyl ketone, ethanol, 10%) (Found: C, 34·3; H, 4·8. $C_{28}H_{46}Cl_4P_2Pt_2$ requires C, 34·4; H, 4·8%).

Bistriethylarsinedichloro-μμ′-dichlorodiplatinum (130—135°, 2 min., acetone, 50% crude) (Found: C, 17·0; H, 3·55. $C_{12}H_{30}Cl_4As_2Pt_2$ requires C, 16·8; H, 3·5%); the *tri*-n-*butyl* analogue (100°, 40 min. but no solidification of melt, ethyl methyl ketone, acetone, 50%) (Found: C, 28·0; H, 5·2%; *M*, ebullioscopic in 1·3% benzene solution, 984. $C_{24}H_{54}Cl_4As_2Pt_2$ requires C, 28·1; H, 5·3%; *M*, 1024).

Bis(di-*n*-propyl sulphide)dichloro-μμ′-dichlorodiplatinum (120°, 15 min., chloroform, 49%) (Found: C, 18·7; H, 3·7. Calc. for: $C_{12}H_{28}Cl_4S_2Pt_2$ C, 18·7; H, 3·7%); the *di*-n-*butyl* analogue (120°, 15 min., chloroform, acetone, 39%) (Found: C, 23·3; H, 4·4. $C_{16}H_{36}Cl_4S_2Pt_2$ requires C, 23·3; H, 4·4%).

Bis(*di*-n-*butyl sulphide*)*dibromo-μμ′-dibromodiplatinum* (120°, 15 min., ethyl methyl ketone, 42%) (Found: C, 19·5; H, 3·7. $C_{16}H_{36}Br_4S_2Pt_2$ requires C, 19·2; H, 3·6%). Bisdiethylsulphidedichloro-μμ′-dichlorodiplatinum is obtained by this method but is difficult to extract from the frozen melt because it is extremely insoluble in all solvents.

Method 2(*a*). We have prepared only two compounds by this method and the preparation of bis(diethyl selenide)dichloro-μμ′-dichlorodiplatinum is typical. *trans*-$[(Et_2Se)_2PtCl_2]$ (3 g.), prepared by shaking Et_2Se (2 mols.) with aqueous K_2PtCl_4 (1 mol.) (Petren, *loc. cit.*), was added to a suspension of Ag_2SO_4 (1·7 g.) in water (100 c.c.). The mixture was warmed to 50° and shaken for 1 hr., then the warming and shaking operation was repeated (about three times) until the selenide complex had dissolved. The mixture was shaken for a further 4 hr. to ensure complete reaction and then filtered to give a brownish-yellow solution. This on addition of K_2PtCl_4 (2·3 g.) in water (25 c.c.) yielded an immediate buff-coloured precipitate which was filtered off after a few minutes. The sticky solid thus obtained was converted into a red-brown solid by drying in a desiccator, and recrystallised from chloroform. The product decomposed at 146—147°. Petren (*loc. cit.*) gives 145° [yield 36%, calc. on the $(Et_2Se)_2PtCl_2$ used] (Found: C, 12·3; H, 2·55. Calc. for $C_8H_{20}Cl_4Se_2Pt_2$: C, 11·9; H, 2·5%). This preparation is a considerable improvement on Petren's original method, but nevertheless the bridged selenides are the most difficult series to prepare. They are very unstable in solution and not easily purified.

Bis(*di*-n-*propyl selenide*)*dichloro-μμ′-dichlorodiplatinum* was prepared similarly from *n*-Pr_2Se and K_2PtCl_4 and purified by dissolving it in a small amount of chloroform, adding some ether, and cooling to −70°. The red-brown powder which separated was washed with ethanol and ether, and dried [yield 10%, calc. on the $(n\text{-}Pr_2Se)_2PtCl_2$ used], decomp. 76·5—77·5° (Found: C, 16·6; H, 3·2. $C_{12}H_{28}Cl_4Se_2Pt_2$ requires C, 16·7; H, 3·3%).

Method 2(*b*). *Bis*(*diethyl sulphide*)*dichloro-μμ′-dichlorodiplatinum*. *cis*-$[(Et_2S)_2PtCl_2]$ (5·3 g.) and Na_2PtCl_4 (4·6 g.) in ethanol (220 c.c.) were kept at 45° for 4 hr. The yellow product which separated was filtered off from the solution, washed with ethanol then water, and dried (yield 73%) (Found: C, 13·3; H, 2·8. Calc. for $C_8H_{20}Cl_4S_2Pt_2$: C, 13·5; H, 2·8%).

Bis(*di*-n-*octyl sulphide*)*dichloro-μμ′-dichlorodiplatinum* is similarly obtained. A solution of Na_2PtCl_4 (0·33 g.) and *cis*-$[(Oct_2S)_2PtCl_2]$ (0·66 g.) in ethanol (30 c.c.) was kept for 24 hr., then at 45° for 6 hr. It was then filtered, and the filtrate taken to dryness at 15° under reduced pressure. The sticky brown residue was recrystallised from ethanol, then acetone (Found: C, 36·1; H, 6·4. $C_{32}H_{68}Cl_4S_2Pt_2$ requires C, 36·6; H, 6·5%).

Bis(*diethyl telluride*)*dichloro-μμ′-dichlorodiplatinum*. A solution of Na_2PtCl_4 (3 g.) and *cis*-$(Et_2Te)_2PtCl_2$ (5 g.) in ethanol (300 c.c.) was kept for several days at room temperature. The crystalline *complex* which formed was filtered off, washed with water, ethanol, and hot ether, and then dried (yield 40·5%) (Found: C, 10·7; H, 2·2. $C_8H_{20}Cl_4Pt_2Te_2$ requires C, 10·6; H, 2·2%).

Bis(*di*-n-*propyl telluride*)*dichloro-μμ′-dichlorodiplatinum* was similarly prepared as a precipitate by keeping a solution of Na_2PtCl_4 (7·4 g.) and *n*-Pr_2Te (4·14 g.) in ethanol for 16 hr. (yield

79%). It was recrystallised from acetone (Found: C, 15·6; H, 3·0. $C_{12}H_{26}Cl_4Pt_2Te_2$ requires C, 15·0; H, 2·9%).

Method 3(*a*). This method is most valuable for the preparation of the trialkylstibine and higher olefin complexes.

Bistrimethylstibinedichloro-μμ'-dichlorodiplatinum. Trimethylstibine (1·3 c.c.) was gradually added, with shaking and under nitrogen, to a solution of $(C_2H_4)_2Pt_2Cl_4$ (3 g.) in acetone (75 c.c.) at −75°. The solution on warming to room temperature and standing overnight deposited the orange crystalline bridged *compound* in poor yield. It was purified by washing it repeatedly with ethyl acetate, then dissolving it in chloroform and reprecipitating it by addition of light petroleum (Found: C, 8·7; H, 2·1. $C_6H_{18}Cl_4Pt_2Sb_2$ requires C, 8·3; H, 2·1%).

Bistriethylstibinedichloro-μμ'-dichlorodiplatinum. Triethylstibine (3·35 g.) in acetone (20 c.c.) was similarly added to $(C_2H_4)_2Pt_2Cl_4$ (4·9 g.) in acetone (60 c.c.) at −75°. The solution, after warming to room temperature and evaporation at 15 mm., left the orange crystalline *complex* which was recrystallised very rapidly from ethyl acetate (yield 35%) (Found: C, 15·3; H, 3·2. $C_{12}H_{30}Cl_4Pt_2Sb_2$ requires C, 15·2; H, 3·2%).

Bistrimethylphosphinedichloro-μμ'-dichlorodiplatinum. Propene platinous chloride (3 g.) in acetone (50 c.c.) was contained in a flask cooled to −70°, and the flask connected to a high-vacuum apparatus. The phosphine [liberated from Me_3P,AgI (3·5 g.) (Mann and Wells, *J.*, 1938, 708)] was then introduced into the flask from the vacuum-apparatus, and the mixture kept for 12 hr. at room temperature. The resulting orange solution was evaporated under reduced pressure to leave a brown gum which solidified on standing. The product was extracted from this with boiling ethyl methyl ketone, treated with a little charcoal, and filtered. The filtrate, taken to dryness under reduced pressure, deposited an orange residue which crystallised in prisms from ethyl methyl ketone and then decomposed at 217—220° (yield 3%) (Found: C, 10·9; H, 2·1. $C_6H_{18}Cl_4P_2Pt_2$ requires C, 10·5; H, 2·7%).

Bis(dimethyl sulphide)dichloro-μμ'-dichlorodiplatinum was prepared by adding dimethyl sulphide (0·7 c.c.) to $(C_2H_4)_2Pt_2Cl_4$ (3 g.) in dichloromethane (50 c.c.) at −70°. The mixture, after warming to room temperature, was evaporated to about 15 c.c., and toluene (35 c.c.) added. When this solution was boiled under reflux, the *complex* separated as a mustard-yellow crystalline solid. It was purified by extracting the impurities with boiling chloroform (yield 66%) (Found: C, 7·7; H, 1·9. $C_4H_{12}Cl_4Pt_2S_2$ requires C, 7·3; H, 1·8%). It is insoluble in all organic solvents tried except boiling ethylene dibromide, from which it crystallises with one tenaciously held molecule of solvent (Found: C, 8·2; H, 1·7. $C_4H_{12}Cl_4Pt_2S_2,C_2H_4Br_2$ requires C, 8·5; H, 1·9%).

An attempt to prepare bis-4-*n*-pentylpyridinedichloro-μμ'-dichlorodiplatinum by this method gave instead cis-*ethylene*-4-n-*pentylpyridinedichloroplatinum*. Ethylene platinous chloride (3 g.) in ethanol (25 c.c.) was cooled to −70°, and 4-*n*-pentylpyridine (1·5 g.) in ethanol (40 c.c) was added gradually with stirring. A yellow precipitate formed immediately, but after the mixture had been kept at −70° for 45 min. and then allowed to warm to room temperature, the precipitate redissolved. The solution was then kept at 60° for 16 hr., filtered from black decomposition products, and cooled to −70°. The white crystalline product which separated was recrystallised repeatedly from ethanol with a small amount of charcoal, and so obtained in silver-white plates, m. p. 142—143° (9%). This compound effervesces when in contact with aqueous potassium cyanide, and is a non-electrolyte in nitrobenzene (Found: C, 32·6; H, 4·4; N, 3·2; Cl, 16·4. $C_{12}H_{19}NCl_2Pt$ requires C, 32·5; H, 4·3; N, 3·2; Cl, 16·0%). The dielectric constant of its benzene solution indicates that it has a *cis*-configuration. In another experiment the yellow precipitate, formed immediately after mixing the reactants, was isolated and found to be *trans*-ethylene-4-*n*-pentylpyridinedichloroplatinum identical with the product described below.

Method 3(*b*). This method is most valuable for the preparation of the amine complexes.

trans-*Ethylenepiperidinedichloroplatinum.* Piperidine (1·2 c.c.) in 3% hydrochloric acid was added to a solution of $K[C_2H_4PtCl_3],H_2O$ (6 g.) in 1% hydrochloric acid (100 c.c.). The solution was carefully neutralised at 0° with 1N-sodium hydroxide, and the yellow precipitate thus obtained filtered off, washed with water, and dried. After repeated recrystallisation from light petroleum (b. p. 60—80°) it had decomp. pt. 100—105° (yield 68%) (Found: C, 22·6; H, 4·0. $C_7H_{15}NCl_2Pt$ requires C, 22·2; H, 4·0%).

Dipiperidinedichloro-μμ'-dichlorodiplatinum. A solution of the above mixed olefin–amine complex in light petroleum (b. p. 60—80°) (400 c.c.) was kept for 2 months, during which orange crystals separated from the solution. These were removed and recrystallised from chloroform (yield 48%) (Found: C, 17·2; H, 3·1; N, 4·0. $C_{10}H_{22}N_2Cl_4Pt_2$

requires C, 17·1; H, 3·2; N, 4·0%). The following pairs of compounds were similarly prepared: trans-*Ethylene*-4-n-*pentylpyridinedichloroplatinum*, thick yellow needles, m. p. 82·5—83·5° (68%) (Found: C, 32·4; H, 4·2. $C_{12}H_{19}NCl_2Pt$ requires C, 32·5; H, 4·3%). *Bis*-4-n-*pentylpyridinedichloro-μμ'-dichlorodiplatinum* (Found: C, 28·8; H, 3·6%; *M*, ebullioscopically in 1·5% benzene solution, 896. $C_{20}H_{36}N_2Cl_4Pt_2$ requires C, 28·8; H, 3·6%; *M*, 831). trans-*Ethylene*-4-n-*nonylpyridinedichloroplatinum*, thick yellow needles, m. p. 73—73·5° (90%) (Found: C, 38·7; H, 5·5. $C_{16}H_{27}NCl_2Pt$ requires C, 38·5; H, 5·5%). *Bis*-4-n-*nonylpyridinedichloro-μμ'-dichlorodiplatinum* (Found: C, 35·4; H, 4·9; N, 3·3. $C_{28}H_{46}N_2Cl_4Pt_2$ requires C, 35·7; H, 4·9; N, 3·0%).

Di-*p*-toluidinedichloro-μμ'-dichlorodiplatinum is obtained only in very small yield. *trans*-Ethylene-*p*-toluidinedichloroplatinum (Chatt, *J.*, 1949, 3340) is not soluble in light petroleum and so its 1% w/v solution in carbon tetrachloride was boiled to effect decomposition. The material underwent a complex decomposition. In general, the solution was boiled under reflux for a convenient time, filtered hot if necessary, and allowed to cool. The solids which separated were collected, and the filtrate boiled again. This was repeated, sometimes as many as twelve times. During about the first 20 hr. of boiling trans-*di*-p-*toluidinedichloroplatinum* separated. This is almost insoluble in all solvents but can be recrystallised with 70% loss from much acetone (Found *: C, 35·0; H, 3·7; N, 5·7; Cl, 14·9; Pt, 40·6. $C_{14}H_{18}N_2Cl_2Pt$ requires C, 35·0; H, 3·8; N, 5·8; Cl, 14·8; Pt, 40·6%). Its *trans*-configuration was proved by Kurnakov's reaction with thiourea (*J. prakt. Chem.*, 1894, **50**, 483). In acetone (50 c.c.) it (0·1 g.) reacted with thiourea (0·13 g., 8 mols.) at room temperature to deposit crystals of trans-*dithioureadi*-p-*toluidineplatinum dichloride*, which recrystallised from water in fine white needles, decomp. 170—180° (Found *: C, 29·65; H, 4·2; Pt, 30·8. $C_{16}H_{26}N_6S_2Cl_2Pt$ requires C, 30·4; H, 4·1; Pt, 30·8%). The cold filtrate from which the *trans*-di-*p*-toluidinedichloroplatinum had been separated was boiled for a further 6—7 hr.; then, on filtering and cooling, a quantity of reddish-orange solid separated (0·16 g.). This was extracted from insoluble *trans*-di-*p*-toluidine-dichloroplatinum with chloroform, the chloroform extract taken to dryness at 15 mm., and the residual trans-*di*-p-*toluidinedichloro-μμ'-dichlorodiplatinum* (0·08 g.) recrystallised from benzene (decomp. 190—205°) (Found *: C, 22·8; H, 2·35%; *M*, cryoscopically in *cyclo*pentadecanone, 704. $C_{14}H_{18}N_2Cl_4Pt_2$ requires C, 22·5; H, 2·4%; *M*, 747). On continued boiling of the carbon tetrachloride reaction mixture under reflux, browner products containing gradually diminishing quantities of *p*-toluidine were obtained. It appeared that a series of compounds of general formula $(C_7H_9N)_2(PtCl_2)_n$ was being produced but they were not easily separated. Fractions soluble in hot chloroform with values of *n* up to 6 were obtained, but this reaction requires further investigation.

The preparation of the bridged *p*-toluidine complex is slightly improved by employing as raw material crude *trans*-propene-*p*-toluidinedichloroplatinum (1 g.), prepared exactly as its ethylene analogue. The carbon tetrachloride solution of the propene complex became orange when boiled under reflux for 5 hr., and after filtration of the *trans*-di-*p*-toluidinedichloroplatinum (0·5 g.) from the hot solution the filtrate deposited the orange bridged complex (0·15 g.) on cooling (Found: C, 22·6; H, 2·5%).

cis-*Di*-p-*toluidinedichloroplatinum* was prepared for comparison with its *trans*-isomer (see above). *p*-Toluidine (0·5 g.), dissolved in a minimum of water, was added to aqueous K_2PtCl_4 (1·0 g.) and kept for two days. The product which separated recrystallised from methanol in pale yellow, felted needles, decomp. 270—280° (Found *: C, 35·1; H, 3·9; N, 5·8; Cl, 15·0; Pt, 40·4%). It is much more soluble in polar organic solvents than its *trans*-isomer, and by Kurnakov's reaction gave yellow tetrathioureaplatinum dichloride, confirming its *cis*-configuration; it had decomp. pt. 240—246° (Found: C, 8·8; H, 2·8. Calc. for $C_4H_{16}N_8Cl_2S_4Pt$: C, 8·4; H, 2·8%).

p-Toluidine complexes $[(C_7H_9N)_2PtCl_2]_n$ have previously been prepared by Gordon (*Ber.*, 1870, **3**, 174) and Cochin (*Compt. rend.*, 1878, **86**, 1402; *Bull. Soc. chim. France*, 1879, **31**, 498), but not completely characterised. From Gordon's method of preparation and the solubility of his product in alcohol his substance was probably *cis*-$[(C_7H_9N)_2PtCl_2]$, but Cochin's compound is insufficiently described to know which isomer it may have been; it was unlikely to be the analogue of Magnus salt, $Pt(NH_3)_4PtCl_4$, which he thought it to be.

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Evidence for Formation of Free-radical Intermediates in Some Reactions involving Periodate.

By M. C. R. Symons.

[Reprint Order No. 6333.]

Reactions are described which indicate that photochemical decomposition of periodate, and reaction of periodate with ferrous ion, occur *via* free radicals, but that certain of its thermal reactions do not.

Of the various known reactions involving periodate species, only those in which α-glycols and related compounds participate have received detailed study. Important amongst the remainder are: the rapid oxidations of malonic acid and related compounds (Hubner, Ames, and Bubl, *J. Amer. Chem. Soc.*, **1946**, **68**, 1621); photodecomposition of aqueous periodate solutions to give iodate and oxygen (Head and Standing, *J.*, 1952, 1457); photo-oxidation of many simple organic compounds (Head and Hughes, *J.*, 1952, 2046); reactions with certain transition-metal ions, for example, the oxidation of manganous salts to permanganate (Waterbury, Hayes, and Martin, *J. Amer. Chem. Soc.*, 1952, **74**, 15); and the reaction with hydrogen peroxide.

As part of a study of the mechanisms of certain of the above reactions now being undertaken in collaboration with Mr. M. G. Brown and Mr. M. Smith, various tests thought to be diagnostic of the presence of active free radicals have been made. The results are summarised in the Table.

Experimental

pH values were measured on a Cambridge pH meter, ultraviolet and visible spectra on a Hilger Uvispek spectrophotometer, and infrared spectra on a Perkin-Elmer spectrophotometer incorporating a lithium fluoride prism for the 2800—3800-cm.$^{-1}$ region.

Acrylonitrile and methyl methacrylate were purified by washing them with, in turn, dilute sulphuric acid, dilute sodium carbonate, and purified water, drying (Na_2SO_4), and distillation under a reduced pressure of oxygen-free nitrogen. Other reagents were of "AnalaR" grade. Water was doubly distilled from strongly alkaline permanganate, and glass apparatus was cleaned with the same reagent. To avoid inhibition of polymerisation by oxygen, monomer solutions were partially frozen and evacuated until vigorous boiling set in. This procedure was repeated several times and proved necessary for the attainment of consistent results. During irradiation experiments, the reduced pressure was maintained in order to lessen the chance of inhibition of polymerisation by any oxygen formed during the decomposition. The pH was adjusted with perchloric acid or potassium hydroxide solutions. Various light sources were used, the most satisfactory being a 125-w high-pressure mercury arc. The irradiated solutions were cooled by a rapid flow of water, and light of wavelength shorter than 3650 Å was largely removed by passage through three layers of soda glass. The times given in the Table represent approximately the interval between the start of irradiation and the separation of flocculent polymer, when the solution was held 9 in. from the arc. This stage was generally preceded by a uniform turbidity throughout the solution. Non-photochemical initiation experiments were carried out as described previously (*J.*, 1955, 273).

In every case temperature, pH, and initial concentration were varied over a wide range. When reactions resulted in polymerisation the optimum concentration of periodate was found to be approx. 10^{-3}M. For polymerisation with ferrous ion concurrent precipitation of a yellow ferric periodate complex masked the appearance of polymer. However, the complex was soluble in excess of perchloric acid, and in M-perchloric acid only polymer separated. For reactions resulting in hydroxylation of benzoic acid, concentrations of potassium periodate and benzoic acid were of the order of 10^{-2}M, and perchloric acid was added to give a pH of about 2. The concentrations are critical in these experiments, since it is necessary to avoid the preferential formation of ferric benzoate or ferric periodate, both of which mask the colour of the ferric salicylate complex formed when ferric chloride is added to the solution. The purple solutions thus obtained had visible and ultraviolet absorption identical with that of an authentic solution of ferric salicylate. When iodate was used in the rôle of periodate in these experiments neither polymerisation nor hydroxylation resulted.

	KIO_4	$CH_2(CO_2H)_2$ or $CHEt(CO_2H)_2$	$(CO_2H)_2$	Fe^{2+}	Cu^{2+}, Mn^{2+}, Fe^{3+}, Co^{2+} *	H_2O_2
	+ CH_2:CH·CN or CH_2:CMe·CO_2Me					
Dark ...	No P.†	No P.	No P.	Rapid P. pH −1 to 4	No P.	No P. pH −1 to 12
Light ...	P. in 30 min. pH −1 to 12	—	P. in 5 min.	—	—	—
	+BzOH					
Dark ...	No reaction	No S.†	No S.	Rapid S., pH 2	No S.	No S.
Light ...	S. in 2 hr., pH 2	—	No S.	—	—	—

* Small yields of polymer were obtained from solutions containing cobaltous ion when exposed to diffused daylight. † P. = polymerisation; S. = formation of salicylic acid.

Samples of polyacrylonitrile for infrared analysis were prepared by pressing about 5 mg. of the powdered polymer, previously dried at $70°/10^{-4}$ mm. for several hr. over P_2O_5, to give a clear film.

Discussion

There seems to be a close parallel between the behaviour of periodate in these reactions and that of hydrogen peroxide in similar reactions (Bates, Evans, and Uri, *Nature*, 1950, **166**, 869; Baxendale, Evans, and Park, *Trans. Faraday Soc.*, 1946, **42**, 155). By inference, it is probable that hydroxyl radicals are formed both in the reaction with ferrous ion and in the photochemical decompositions. It was hoped that infrared analysis of the polyacrylonitrile formed during these experiments might reveal the presence of hydroxyl end groups (Dainton, *J. Phys. Colloid Chem.*, 1948, **52**, 490), but the results are not conclusive. In all of six analyses, slight, broad, absorption between 3100 and 3400 cm.$^{-1}$ was found, characteristic of hydrogen-bonded hydroxyl groups. In all cases, however, some absorption was also found in the 3600-cm.$^{-1}$ region, indicative of non-hydrogen-bonded hydroxyl groups, and an unidentified band at 1625 cm.$^{-1}$ which might be caused by water. However, since prolonged heating under a high vacuum did not significantly reduce the intensity of the 3600-cm.$^{-1}$ band, this explanation seems unlikely. Definite absorption between 1650 and 1750 cm.$^{-1}$, probably caused by carbonyl groups, was always found. These groups could have been formed either by hydrolysis of cyanide groups, or by oxidation of primary alcoholic end-groups by the irradiated periodate. The former alternative is improbable under the conditions used. In accord with this, it was found that the carbonyl absorption spectrum of a sample of polyacrylonitrile, formed by irradiation of an acidic periodate solution, was unchanged when a portion was left in contact with the parent solution for twelve hours in the dark.

Croutamel, Hayes, and Martin (*J. Amer. Chem. Soc.*, 1951, **73**, 82) found that neutral periodate solutions have a broad absorption peak at 2225 Å, which they assign to the anhydrous ion IO_4^-. This was also found by Head and Standing (*J.*, 1952, 1457), who remarked on the fact that periodate solutions are readily decomposed by light of wavelength far removed from this value. However, in comparison with the absorption curves of other oxy-ions, that of neutral periodate solutions is remarkably broad, with a tail in the near ultraviolet somewhat resembling that of hydrogen peroxide (Symons and Smith, unpublished results). It is tentatively suggested that, whilst the peak at 2225 Å may be characteristic of the IO_4^- ion, being possibly a result of charge transfer to the solvent sheath (Platzman and Franck, *Z. Physik*, 1954, **138**, 411), the long tail may be associated with the hydrated ion $H_4IO_6^-$, which is thought to be the photochemically active species.

Although quantum yields for the photochemical decomposition have not yet been measured, it seems probable that they will be considerably greater than the low values normally found for reactions in solution, owing to the operation of the primary dark back-reaction (Frank and Rabinowitsch, *Trans. Faraday Soc.*, 1934, **30**, 120). A chain mechanism is therefore provisionally postulated, which may, for the $H_4IO_6^-$ ion, be formulated as

$$H_4IO_6^- + h\nu \rightleftharpoons H_3IO_5^{\cdot-} + {\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$H_3IO_5^{\cdot-} \longrightarrow IO_3^- + H_2O + {\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$H_4IO_6^- + {\cdot}OH \rightleftharpoons H_2O_2 + H_3IO_5^{\cdot-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$H_4IO_6^- + H_2O_2 \longrightarrow IO_3^- + 3H_2O + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Reaction (2) is a thermal breakdown of the I^{VI} compound, and reactions (2) and (3) represent a chain process for the formation of iodate and hydrogen peroxide. Reaction (4) is a rapid dark reaction, which probably proceeds without the intermediate formation of radicals (see Table). An alternative route, involving the photodecomposition of hydrogen peroxide, and the resulting initiation of further decomposition of the periodate, is considered to be less probable.

In accord with the postulate that it is the hydrated ion which is photochemically active and the source of free radicals is the observation that polymerisation is still induced under acidic and alkaline conditions, when respectively the iodine is largely present as H_5IO_6 and $H_3IO_6^{2-}$ (Croutamel *et al.*, *loc. cit.*).

When oxalic acid is added to periodate solutions, there is a marked shift in the absorption peak at 2225 Å (Brown and Symons, unpublished results) which is thought to be indicative of complex formation. Such a complex, particularly if it is cyclic, could readily break down by a simple electronic shift to give iodate and carbon dioxide, and this may well be the mechanism of the slow thermal decomposition. However, these results show that the relatively rapid photodecomposition is a ready source of active free radicals and does not proceed by the above mechanism. In fact, polymerisation is induced far more readily by irradiation of periodate solutions in the presence of oxalic acid than in its absence, and it therefore seems probable that the photochemically active species is an oxalic acid–periodate complex. However, the photo-oxidation of simple alcohols, aldehydes, etc. (Head and Hughes, *loc. cit.*), may occur by initial formation of hydroxyl radicals.

Again by analogy with hydrogen peroxide, the reaction with ferrous ion is thought to involve hydrated periodate, being pictured as an electron-transfer reaction of the type

$$Fe^{2+} + H_4IO_6^- \rightleftharpoons FeOH^{2+} + H_3IO_6^{\cdot -} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$H_3IO_6^{\cdot -}$ may break down as in (2), either at the time of electron transfer or later, to give a free hydroxyl radical which can initiate polymerisation or hydroxylate benzoic acid. However, dropwise addition of ferrous sulphate solution to an excess of periodate did not result in oxygen evolution.

Whenever polymerisation did not occur the reductant underwent an overall valency change greater than one, and there is no compelling reason for postulating radical intermediates. Thus, the reaction with hydrogen peroxide may be pictured as involving a peroxy-compound formed by addition of the peroxide to the IO_4^- ion, followed by breakdown to give iodate and oxygen. Thus the rôle of the periodate is that of an acceptor, as is postulated in glycol fission reactions—a rôle for which it is particularly suited because of the ready availability of the outer *d*-orbitals of the iodine for bonding (Symons, *J.*, 1954, 3676).

When malonic acid is oxidised by manganic pyrophosphate, which is a one-electron acceptor only, organic radicals are formed, and can be detected by the polymerisation test (Drummond and Waters, *J.*, 1954, 2456) : thus it can be concluded that such radicals are not involved in periodate oxidations of malonic acid, and therefore that two distinct mechanisms are involved. It is hoped that a kinetic study, now in progress, will shed light on this mechanism.

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*The Conductivity of Silver Nitrate in Non-aqueous and Mixed Solvents. Part III.**

By V. S. Griffiths and K. S. Lawrence.

[Reprint Order No. 6165.]

The conductivity of silver nitrate in acetone solutions containing pyridine, the three picolines, quinoline, or γ-collidine is reported and discussed.

It is usually accepted that the dissociation of an electrolyte is dependent on two factors, namely, the dielectric constant of the medium and the ionic radii, and many attempts have been made to study the effects of these variables separately. As far as the dielectric constant is concerned, it is usual to assume that no changes in solvation occur, and that the bulk dielectric constant controls the association–dissociation process (see James, *J.*, 1950, 1094; 1951, 153). Where the ionic radii are concerned it is general to calculate the value of the radii from the use of Stokes's hydrodynamics or to consider the "***a***" parameter of the Bjerrum–Fuoss treatment (*Kgl. Danske Vidensk. Selskab*, 1926, **7**, No. 9; *J. Amer. Chem. Soc.*, 1933, **55**, 1019) which assumes that purely electrostatic forces are involved in the formation of ion-pairs.

Hasted, Ritson, and Collie (*J. Chem. Phys.*, 1948, **16**, 1) have shown that at distances less than 4 Å from an ion, the dielectric constant is a rapidly varying quantity and it appears doubtful whether the bulk dielectric constant should be used in these calculations. In a recent series of papers Fuoss and his co-workers (*J. Amer. Chem. Soc.*, 1950, **72**, 301; 1953, **75**, 3076, 5172; 1954, **76**, 5897, 5902, 5905) have criticised the so-called "sphere-in-continuum" model used to describe electrolytic solutions, and a tentative solution has been proposed involving the breakdown of solvent structure in the case of solvents which associate in the pure form, but as yet it appears that each solvent mixture must be treated on its own merits. According to Fuoss *et al.*, the formation of an ion-pair is described by the approach of two ions through the solvent until only one molecule, the solvate molecule, separates them. This is then followed by a further separate step in which the solvate molecule is expelled. It is emphasised that in this process the dielectric constant will vary from its bulk value to that obtaining at electrical saturation, as the two ions approach.

Grunwald (*Analyt. Chem.*, 1954, **26**, 1696) discusses the fact that the removal of the single solvate molecule from the ion-pair will need very considerable energy. Further, he points out that in polar solvents the ions exist in a solvation sheath, the radius of which has been estimated to be about 5 Å. Thus, if both ions are solvated to this extent, when the interionic distance is less than 10 Å the solvation shells overlap, and this overlapping will occur at the expense of solvation energy. This energy change may well go to offset the effect of changing dielectric constant near the ions owing to electrical saturation.

It thus seems necessary to consider the conductivity of electrolytes in different solvents in terms of changing dielectric constant, and ionic size in terms of specific solvent–solute interaction, remembering that in binary mixtures of solvents the addition of the second component may modify the structure of the other component with consequent changes in solvation.

It would appear that systems containing the Ag^+ ion should give much useful information, since it has been shown that this ion interacts strongly with certain organic molecules owing to its electron-accepting properties (see Griffiths, *J.*, 1954, 686). Further, silver nitrate in acetone is a very weak electrolyte (see Griffiths and Lawrence, *J.*, 1955, 1208; Ross-Kane, *Ann. Reports*, 1930, **27**, 340) and it was thought that if small quantities of solvents possessing electron-donating properties were added to such solutions, then the latter should interact strongly with the Ag^+ ion, giving a larger ion and possible increase in the degree of dissociation, whilst the bulk dielectric constant would not be altered

* Part II, *J.*, 1955, 1208.

appreciably. To this end the conductivity of silver nitrate in acetone solutions containing traces of organic bases was measured.

Results. These are shown in tabular and graphical form. In the Tables, c is the molar concentration of silver nitrate, and the weight percentages in Table 2 correspond to 0·0735 mole % of base in acetone.

TABLE 1.

0·1% *Pyridine*

10^4c	Λ	10^4c	Λ	10^4c	Λ
0·2620	150·9	1·275	104·3	2·109	88·69
0·5477	130·7	1·461	100·0	2·388	84·98
0·7616	120·5	1·658	96·09	2·693	81·47
1·054	110·3	1·873	92·32	3·368	75·09

$\Lambda_0 = 193{\cdot}7$; $K = 0{\cdot}754 \times 10^{-4}$.

1·0% *Pyridine*

10^4c	Λ	10^4c	Λ	10^4c	Λ
0·2302	164·6	1·202	123·9	2·980	96·66
0·4268	149·9	1·642	114·6	2·922	95·31
0·5696	144·3	1·709	111·8	3·854	89·09
0·7659	136·3	2·167	106·3	4·070	85·45
0·8567	132·9	2·257	103·2		

$\Lambda_0 = 188{\cdot}9$; $K = 1{\cdot}42 \times 10^{-4}$.

TABLE 2.

0·118% α-*Picoline*

10^4c	Λ	10^4c	Λ	10^4c	Λ
0·1265	169·9	0·5765	131·6	1·060	112·5
0·2626	153·4	0·7385	123·9	1·305	105·8
0·3926	142·9	0·8336	120·1	1·514	101·1
0·4980	135·9	0·9195	117·0	1·798	95·69

0·118% β-*Picoline*

10^4c	Λ	10^4c	Λ	10^4c	Λ
0·2218	157·4	1·085	110·9	1·706	96·76
0·4174	139·7	1·230	107·0	1·881	93·76
0·6751	125·7	1·398	102·9	2·149	89·69
0·8713	117·8	1·580	99·14	2·641	83·59

0·118% γ-*Picoline*

10^4c	Λ	10^4c	Λ	10^4c	Λ
0·1665	169·1	0·8033	132·0	1·451	114·2
0·3069	156·0	0·9630	126·7	1·575	111·6
0·4850	145·7	1·148	121·4	1·746	108·4
0·6452	138·2	1·292	117·8	2·007	104·1

0·153% γ-*Collidine*

10^4c	Λ	10^4c	Λ	10^4c	Λ
0·07526	178·3	0·4038	152·9	0·7742	139·8
0·1638	170·3	0·4924	148·5	0·9303	131·8
0·2336	164·8	0·5971	143·7	1·096	126·9
0·3253	157·4	0·7027	139·5	1·311	121·7

0·163% *Quinoline*

10^4c	Λ	10^4c	Λ	10^4c	Λ
0·1821	147·9	0·5044	120·0	0·8421	104·7
0·3670	129·1	0·6948	110·5	0·9276	101·7
1·129	95·86	1·414	89·11	1·776	82·47
1·220	93·49	1·567	86·07	2·147	77·09

Discussion.—Shedlovsky's extrapolation method (*J. Franklin Inst.*, 1938, **225**, 739) was used to calculate the values of Λ_0 and K for the electrolyte solutions. The viscosities of the mixtures containing the bases were taken to be those of acetone, since additions of up to 0·5% of base did not give viscosity variations which were detectable by ordinary techniques. In the first instance, where any data were available, a linear relation was assumed to hold between dielectric constant of the solvent mixtures and their composition, but it was found that, with the concentration of base added, there was little difference from the value holding for the dielectric constant of acetone. It was thus decided to use the constants for acetone for the solvent mixtures.

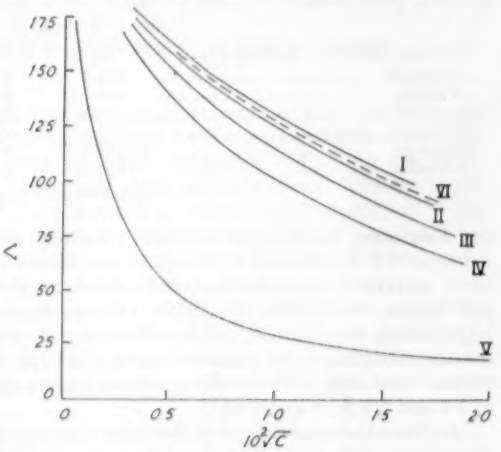
It was found that, whilst the addition of a small percentage of pyridine considerably increased the equivalent conductivity, the effect of greatly increasing this concentration had little further effect (see curves III and VI). Since it is reasonable to expect that the cation will be solvated by the base whilst the anion will be little solvated (see Ulich, *Trans. Faraday Soc.*, 1927, **23**, 388) it would be expected that the mobility of the cation would be decreased as compared with the mobility in acetone, leading to a decrease in conductivity on addition of a little pyridine. It thus appears that the expected fall in conductivity due to the formation of the complex cation must be more than nullified by some larger effect acting in the opposite sense, and it is suggested that this is an increase in the degree of dissociation of the electrolyte. In acetone the dissociation constant of $AgNO_3$ is approx. 4×10^{-6}, whilst in solutions containing 0·1% of pyridine the dissociation of the complex is $0{\cdot}75 \times 10^{-4}$ (Table 3). It is noteworthy that in the case of the latter solutions the extrapolation plots are linear as compared with those obtained for pure acetone which show marked deviations from linearity much below Fuoss's critical concentration (*J. Amer. Chem. Soc.*, 1935, **57**, 2604; see also Griffiths and Lawrence, *Research*, 1953, **6**, No. 11).

The value of Λ_0 remains substantially of the same order as in pure acetone even though the value of K is greatly increased, suggesting that the latter is responsible for the increase in conductivity.

The other bases used showed characteristics similar to those of pyridine, the actual magnitude of the effects produced being illustrated in the figure, where all the base concentrations are of the same molar %, and are equivalent to a 0·1% w/w solution of pyridine in acetone. The mixtures containing quinoline showed a smaller conductivity than those containing pyridine, possibly owing to the lower cationic mobility of the quinoline–silver complex. On the grounds of size alone, equal numbers of molecules of base being assumed to be attached to the silver ion, it might be expected that γ-collidine would have the lowest

Conductivity of silver nitrate in mixed solvents.

(I) γ-Collidine and acetone.
(II) γ-Picoline and acetone.
(III) Pyridine and acetone (and α- and β-picoline and acetone).
(IV) Quinoline and acetone.
(All 0·0735 mole % of first-named solvent.)
(V) Pure acetone.
(VI) 1% (w/w)Pyridine in acetone.



conductivity. It is found that this is not the case (see Figure), and the reason is probably to be found in the fact that this system gives the largest K value of the group studied. It is possible in this instance that the ion–solvent interaction is very strong owing to the stronger basic nature of γ-collidine. The α- and β-picolines showed results very similar to those obtained with pyridine, but with γ-picoline a larger dissociation constant was obtained than with either of the other picolines or pyridine, and this might be accounted for by an effectively larger ion in the case of the γ-picoline–silver complex. It is of interest to compare the sequence of the strengths of the bases involved with the sequence of the dissociation constants for silver nitrate in the acetone solutions containing the bases.* A review of the data for the base strengths in water shows the following sequence: Quinoline = pyridine < β-picoline = γ-picoline < α-picoline < γ-collidine (Remick, "Electronic Interpretations of Organic Chemistry," 2nd Edn., Chapman and Hall, 1949, p. 301; Conway, "Electrochemical Data," Elsevier Publ. Co., 1952, p. 186; Heilbron, "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1934), whilst the order of the dissociation constants for silver nitrate in acetone containing these bases is: Quinoline < pyridine < α-picoline = β-picoline < γ-picoline < γ-collidine. It can be seen that there is some similarity between these two series but since different solvents are involved, namely, water and acetone, it is perhaps inadvisable to draw too many conclusions from these comparisons.

From a consideration of Walden's rule (*Z. phys. Chem.*, 1906, **55**, 207; 1912, **78**, 257) taken in the form

$$\lambda_0^{\pm}\eta_i = \frac{e\mathbf{F}}{6\pi}\left(\frac{1}{r^{\pm}}\right)$$

where λ_0 is the ionic mobility, η_i the viscosity, and $r^{\pm}$ the radius of the positive or negative ion, it might be expected that any large change in the value of the apparent ion-radius r

* We thank a referee for this suggestion.

would show a corresponding change in $\lambda_0\eta$. The nitrate ion has been shown to be little solvated by pyridine (Ulich, *loc. cit.*), and thus the value for its mobility in acetone was taken to hold for the solvent mixtures considered. Davies (" Conductivity of Solutions," 2nd Edn., Chapman and Hall, London, 1933, p. 207) gives a value of 120, and Λ_0 for silver nitrate in acetone being taken as 206, $\lambda_0^+\eta = 0{\cdot}268$. Turning to the solutions containing the bases, the $\lambda_0^+\eta$ product decreased, indicating an increase in r, the greatest value of r being obtained for quinoline, as might be expected if there has been interaction between the cation and the relatively large base molecule.

Table 3 also shows the values of Bjerrum and Fuoss's " a " parameter (*loc. cit.*), and although these show some increase over the value holding in pure acetone (1·5 Å, Griffiths

TABLE 3.

Solvent mixture : acetone plus	Λ_0	10^4K	$\lambda_0^+\eta$ *	a, Å	10^8r^+ (cm.)
γ-Collidine	188·3	1·49	0·218	2·15	3·94
γ-Picoline	189·7	1·26	0·213	2·17	3·89
Pyridine	193·7	0·75	0·225	2·00	3·62
α-Picoline	194·1	0·81	0·226	2·01	3·62
β-Picoline	192·9	0·80	0·223	2·01	3·67
Quinoline	184·7	0·60	0·197	1·94	4·12

* η is the viscosity of the solvent.

and Lawrence, *loc. cit.*), the increase was not as great as was expected in view of the large value of 6·6 Å obtained by Burgess and Kraus (*J. Amer. Chem. Soc.*, 1948, **70**, 706) for silver nitrate in pure pyridine, and 5·78 Å for the same salt in ammonia at −33° (Fuoss and Kraus, *ibid.*, 1933, **55**, 1019). It was assumed by these authors that a relatively large cation was formed, whose effective size was then increased by further solvation. On the other hand, the data of Martin (*J.*, 1928, 3270) and of Walden and Birr (*Z. phys. Chem.*, 1929, **144**, 269) for silver nitrate in benzonitrile and acetonitrile give " a " values of 1·6 and 1·9 Å, respectively.

In these circumstances it is doubtful if any quantitative significance can be attached to these " a " values, further than that they indicate the distance between the centres of ionic charge if purely electrostatic forces prevail. It is felt that since sufficient base was added to the solution to solvate all the silver ions, then the use of Stokes's hydrodynamics gives a better estimate of the ion-size as far as this work is concerned. From Table 3 it can be seen that the larger the r value the larger the dissociation constant K, except in the case of solutions containing quinoline. Here a large ion is indicated, though the value of K is the smallest recorded, and it is suggested that this may be the result of the Ag^+ ion's interacting with one quinoline molecule, while in the other mixtures it is probable that complex ions of the type $Ag(py)_2^+$ exist (see Woodman and Corbet, *J.*, 1925, **127**, 2461; Schmidt and Keller, *Z. phys. Chem.*, 1929, **141**, *A*, 331; Britton and Williams, *J.*, 1935, 798). It thus appears that in the mixtures investigated the dissociation of the electrolyte is largely governed by the ionic size, although it is considered that in general each case must be considered on its own merits.

Experimental.—Procedure. This was as previously described (Griffiths and Lawrence, *loc. cit.*). Conductivities of the solvent mixtures were not materially different from that of pure acetone and solvent corrections were applied in the normal way.

Materials. The acetone and pyridine were purified by the method described by Griffiths (*J.*, 1952, 1326) and the physical constants used were those given by him (*J.*, 1954, 686). The other bases were treated by repeated fractional distillation and had the following b. p.s at normal atmospheric pressure : α-picoline, 130°; β-picoline, 144°; γ-picoline, 143°; γ-collidine, 172°; quinoline, 237°. They were sealed under nitrogen in glass ampoules until required.

The authors thank the Morgan Crucible Co. Ltd. for a scholarship to one of them (K. S. L.), to the Central Research Fund of the University of London for a grant to the other (V. S. G.), and to Imperial Chemical Industries Limited for a grant for glassware and cells.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, February 22nd*, 1955.]

The Stereoisomerism of Addition Polymers. Part I. The Stereochemistry of Addition and Configurations of Maximum Order.

By C. L. Arcus.

[Reprint Order No. 6224.]

Configurations for linear polymers which contain asymmetric carbon atoms have been deduced from a consideration of the steric factors in olefinic addition.

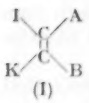
Diastereoisomeric forms arising from mutual chain termination are described.

The experimental data relevant to the method of derivation, and to polymer configurations, are discussed.

The possibility of optical isomerism, including diastereoisomerism, in addition polymers containing asymmetric carbon atoms has been recognised for a considerable time (Marvel, Frank, and Prill, *J. Amer. Chem. Soc.*, **1943**, **65**, 1647; Huggins, *ibid.*, **1944**, **66**, 1991; Marvel and Overberger, *ibid.*, **1946**, **68**, 2106), and more recently Frisch, Schuerch, and Szwarc (*J. Polymer Sci.*, **1953**, **11**, 559) have presented a mathematical treatment of the possibility of continued partial asymmetric synthesis during addition polymerisation.

A method for the derivation of chain configurations, based on the control of the stepwise addition of monomer molecules by three steric factors, is now put forward. The chain configurations which are possible in the general case of polymerisation of a fully substituted ethylene are deduced, and from these, by simplification, those for less substituted ethylenes [Section (1)]. In Section (2), data in the literature concerning the stereochemistry of addition and configurations of polymers are discussed in relation to the configurations derived as above.

(1) *Derivation of Configurations of Maximum Order.*—Polymerisation of the olefin (I) is considered to be initiated by the formation of an intermediate (II) which has substantial steric stability; the initiating radical or ion, R, is bonded to both the carbon atoms of the original double bond, and the structure is perpendicular to the plane occupied by the groups I, A, K, B. The evidence for such structures is summarised in Section (2). A similar intermediate is formed during the addition of each successive molecule of monomer, when R becomes the tail carbon atom of the penultimate monomer unit. Head-to-tail (>CKB to >CIA) polymerisation, only, has been considered.

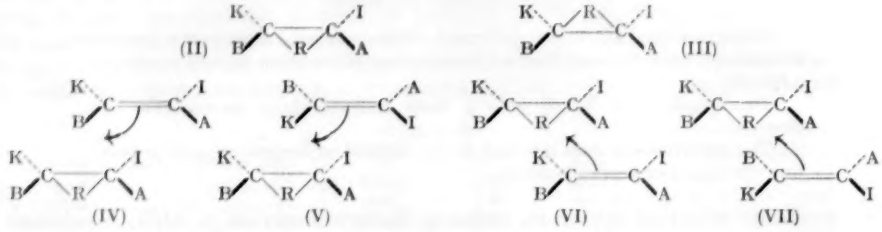


(I)

The experimental evidence [Section (2)] indicates that addition, whether ionic or free-radical, is normally *trans*; however, for completeness, configurations derived by *cis*-addition have been included. It has been assumed that, in any individual polymerisation, reaction is either *trans* at every step or *cis* at every step.

In addition to the possibility of *trans*- or of *cis*-reaction, two alternative steric courses are possible for the reaction of a second molecule of monomer with the radical or ion derived from the first. This may proceed by either of the two modes of presentation represented in (IV) and (V) for *trans*-, and in (VI) and (VII) for *cis*-addition. At the time of reaction the two molecules are in close contact and overlap to a substantial extent; the distances between the groups I, A, K, B, on the second and those on the first molecule are not the same for the two modes of presentation; the net interaction of these groups will, in general, differ for the two modes, and reaction will proceed more readily by one than by the other. (Reactions by the two modes of presentation become equally probable only when an axially symmetrical olefin, $CA_2{:}CB_2$, is undergoing polymerisation.) For any individual polymerisation it has been assumed that, at each step, a monomer molecule takes up the same presentation to the monomer unit which comprises the end of the growing chain. The presentation shown in (IV) and (VI) is referred to as mode [1] and that shown in (V) and (VII) as mode [1′].

Finally, in the Fischer projection formulæ of the polymeric chains derived from (IV)—(VII), the first group B lies to the right. Initial attack by the radical or ion R at the other side of the olefin molecule is equally probable, and the adduct so formed (III) gives rise to a series of polymeric chains enantiomeric with those derived from (IV)—(VII). The two series of chains are designated *D* and *L* respectively.



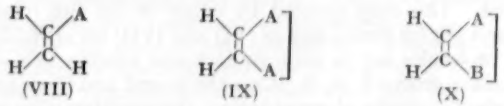
There are thus three stereochemical factors, *trans*- or *cis*-addition, presentation, configuration of initiation, which directly affect the configuration of a chain formed by addition polymerisation. Each presents two alternatives, and eight configurations are possible to a polyethylenic chain derived from the monomer (I). These configurations are represented by the Fischer formulæ (1—8), which arise as follows :

Addition	Mode of presentation	*D*-Initiation	*L*-Initiation
trans	[1]	(1)	(5)
trans	[1′]	(2)	(6)
cis	[1]	(3)	(7)
cis	[1′]	(4)	(8)

Configurations for other polymerisations, of types more frequently encountered experimentally, have been derived (below) by simplification of (1—8). For greater clarity the groups I and K have been omitted in (1—8), they can in every instance be written in from the positions of A and B; in the derived configurations (9—20) hydrogen has likewise been omitted.

On inspection of the chains (1—8) from their points of initiation, it is apparent that there are four pairs of enantiomers, each pair diastereoisomeric with the others. If sections of these chains, of indefinite length and remote from the end-groups, are considered, configurations (1), (4), (5), (8) have a plane of symmetry at every carbon atom, and (2), (3), (6), (7) have no plane of symmetry. Further, comparison of such sections (without regard to the terminal sections of the chains) shows that (2), (3), (6), (7) are identical, as are (1) and (5), also (4) and (8). These identities become important if attempts are made to correlate *X*-ray crystallographic structures (which are essentially for such isolated chain-sections) with mechanisms of polymerisation.

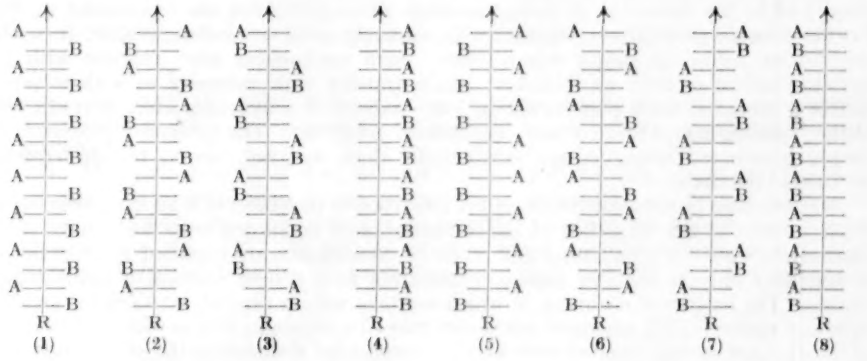
Polymerisation of $CH_2{:}CHA$ (*and of* $CH_2{:}CIA$). Monomer (I) is replaced by (VIII); forms (1—8) lead to only four different configurations : (1), (8) ⟶ (9); (2), (7) ⟶ (10);

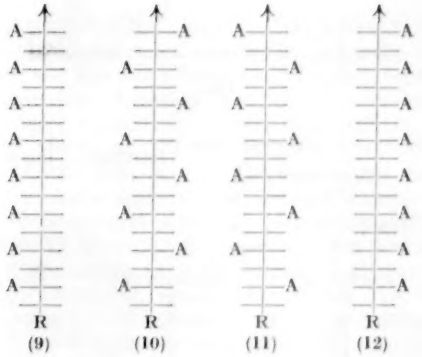


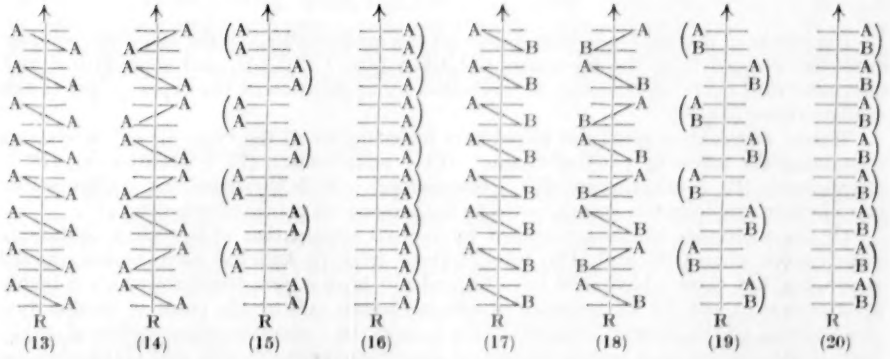
(3), (6) ⟶ (11); (4), (5) ⟶ (12); of these (9) and (12), (10) and (11) are enantiomers. When non-terminal sections of the chains are compared it is found that (9) and (12) possess a plane of symmetry at every carbon atom, and are identical, and that (10) and (11) have a plane of symmetry at every >CHA group, and are identical. The configurations derived from the polymerisation of $CH_2{:}CIA$ are (9—12), except that the groups >CHA are replaced by >CIA.

Polymerisation of a symmetrical cyclic olefin. The configurations (*e.g.*, for the linear

polymerisation of acenaphthylene) are derived by replacing (I) by (IX); forms (1—8) lead to four pairs of enantiomers of which the *D*-forms are represented in (13—16). On inspection of non-terminal sections of the chains, it is seen that: (13) and its enantiomer have no plane of symmetry and are not identical; (14) and its enantiomer have planes of







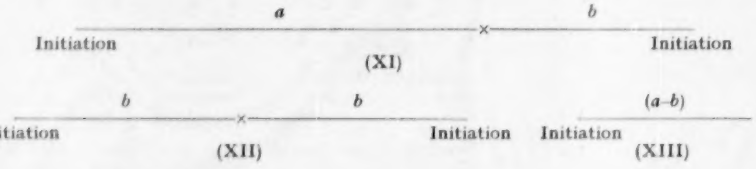
symmetry between the rings, and are identical; (15) and its enantiomer have planes of symmetry across the centres of the rings, and are identical; (16) and its enantiomer have planes of symmetry across the centres of the rings and between the rings, and are identical.

Polymerisation of a non-symmetrical cyclic olefin. The configurations (*e.g.*, for the linear polymerisation of indene) are obtained by replacing (I) by (X); four pairs of enantiomers

are given of which the *D*-forms are represented in (17—20). Non-terminal sections of these chains possess no plane of symmetry, but such sections of (18) and its enantiomer are identical, as are those of (19) and its enantiomer, whereas those of (17) and enantiomer, and (20) and enantiomer, are not identical.

Effects of termination reactions on stereoisomerism. A number of mechanisms of termination lead to the formation of chain molecules whose structures are represented by the Fischer formulæ given above, together with relatively small terminating groups; these are referred to, below, as simple terminations. Such mechanisms are: reaction with an initiator radical or with an inhibitor; chain transfer with monomer or with solvent; loss of a proton in ionic polymerisation; the transfer of a hydrogen atom between two chains, yielding one saturated and one olefinic end-group. The symmetry properties of simply terminated molecules are substantially those assigned, above, to non-terminal portions of the chains.

Mutual chain termination results in the formation of molecules of several stereoisomeric types. Since, in the derivation of the configuration of maximum order for a given polymerisation, *trans*- or *cis*-addition and mode of presentation are regarded as constant, it is necessary only to consider mutual termination in a system containing enantiomeric chains. The lengths of chains (*a*, *b*) which combine will, in general, be different, and the resultant molecule (XI) approximates in structure to a molecule (XII) in which two sections of length *b* are united, together with a simply terminated molecule (XIII) of length (*a*—*b*).



Four types of chain arise:

			(XI)	
Type	Initiation of *a*	Initiation of *b*	(XII)	(XIII)
(i)	*D*	*D*	*DD*	*D*
(ii)	*D*	*L*	*DL*	*D*
(iii)	*L*	*D*	*LD*	*L*
(iv)	*L*	*L*	*LL*	*L*

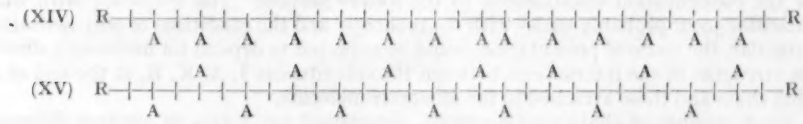
The effects of mutual chain termination on the configurations of the complete polymer molecules derived from the monomers CH_2:CHA (also CH_2:CIA), and symmetrical and unsymmetrical cyclic olefins, may be evaluated by application of the types (i—iv) to the configurations (9—20).

Mutual termination gives rise to polymer molecules of all the types (i—iv) in systems containing the following pairs of chains: (13 + enantiomer), (17 + enantiomer), (18 + enantiomer), (19 + enantiomer), (20 + enantiomer). With the remaining configurations considerable simplification occurs, owing to the presence of planes of symmetry.

Of the molecules which are formed by mutual termination in a system containing enantiomeric chains (9) and (12), those derived from (i) and (iv) have no exceptional symmetry, but those which arise from (ii) and (iii) have a *meso*-structure which is highly symmetrical except for the presence of one tail-to-tail unit at the point of combination [for example, (XIV), derived from (ii)]. The system (16 + enantiomer) resembles (9 + 12). Mutual termination in a system containing enantiomeric chains (10) and (11) yields, for all types of combination (i—iv), a highly symmetrical *meso*-type of molecule. It is irregular only in that a tail-to-tail unit is present and, in the molecules derived from (i) and (iv), an uncompensated unit at one end of the molecule [for example, (XV), derived from (i)]. The systems (14 + enantiomer) and (15 + enantiomer) resemble (10 + 11).

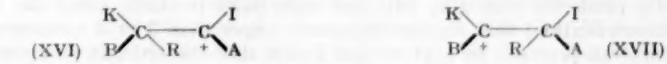
Owing to the symmetry of the monomer, there is no structural irregularity at the point

of mutual termination in those systems (13—16 and enantiomers) which are derived from (IX). Half of the molecules formed from (14 + enantiomer) and (15 + enantiomer) are



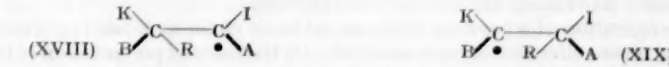
sterically regular at this point, in the remainder a steric irregularity occurs; the molecules which arise from (16 + enantiomer) by (ii) and (iii) are all sterically regular at the point of termination.

(2) *The Stereochemistry of Addition, and Recorded Polymer Configurations.*—It appears to be generally accepted that cationic intermediates of type (II) are formed during ionic addition to olefins; such a structure was originally proposed by Roberts and Kimball (*J. Amer. Chem. Soc.*, 1937, **59**, 947) for bromine addition. The cationic form of (II) is considered to be stabilised by resonance between (XVI) and (XVII). The subsequent



addition of a nucleophilic reagent to the complex cation is *trans* to the group R; McKenzie's results (*J.*, 1912, **101**, 1196) demonstrate *trans*-addition for the reaction of bromine with fumaric and maleic acids, and those of Winstein and Lucas (*J. Amer. Chem. Soc.*, 1939, **61**, 1576, 2845), on the conversion of *erythro*- and *threo*-3-bromobutan-2-ol into *meso*- and racemic 2 : 3-dibromobutane, respectively, require *trans*-addition to a complex cation of type (II). It is inferred, therefore, that cationic polymerisation proceeds by a series of *trans*-additions. In the initial step, R is (in the majority of examples) a hydrogen ion formed by reaction of the electrophilic reagent (boron trifluoride, titanium tetrachloride, stannic chloride) with the co-catalyst (water, trichloroacetic acid) [literature reviewed by Bawn (*Ann. Reports*, 1950, **47**, 36) and by Collinson, Dainton, and Ivin (*ibid.*, 1953, **50**, 62)]; examples of styrene polymerisation have been reported in which R is an alkyl cation (Plesch, *J.*, 1953, 1664). Thereafter, successive monomer molecules function as nucleophilic reagent and R becomes the tail carbon atom of the penultimate unit.

The free-radical addition of hydrogen bromide to 1-bromo- and 1-methyl-*cyclo*hexene has been shown by Goering, Abell, and Aycock (*J. Amer. Chem. Soc.*, 1952, **74**, 3588) to be *trans*. These authors propose a resonance-stabilised intermediate of type (II; R = Br). For olefinic polymerisation, where R is at first the initiator radical and thereafter the penultimate tail carbon atom, the contributing forms are (XVIII) and (XIX).



The literature on the hydroxylation of olefins has little relevance to the stereochemistry of free-radical addition because in no instance are both the steric course and a free-radical mechanism established. Mugdan and Young (*J.*, 1949, 2996) have collected the recorded steric results for the hydroxylation of olefins by hydrogen peroxide in the presence of osmium tetroxide and pervanadic and pertungstic acid; neglecting doubtful cases, they find that catalysis by osmium tetroxide results in *cis*-addition of hydroxyl groups, and that addition in the presence of the per-acids is *trans*. These authors reject mechanisms of addition by hydroxyl radicals in favour of reaction *via* a cyclic osmic ester (Criegee, *Annalen*, 1936, **522**, 75) and, for the per-acids, either epoxide formation or ionic addition of the per-acid itself. Reaction *via* hydroxyl radicals does not appear to contribute extensively to oxidation by dilute alkaline permanganate (Kenyon and Symons, *J.*, 1953, 3580), whence steric results obtained with this reagent are probably not relevant to free-radical addition.

The polymer configurations which have been derived, above, are those of maximum

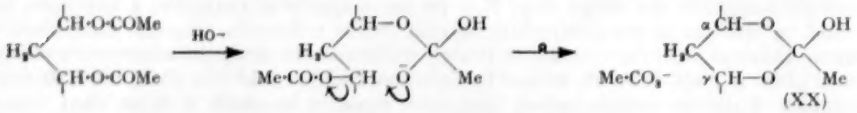
order; if, at intervals, a monomer molecule is added irregularly, either as regards *trans*- (or *cis*-) addition, or with regard to mode of presentation, then thereafter the chain will follow the configuration enantiomeric to the former section. The frequency with which irregularities occur probably varies with the monomer and the conditions of polymerisation; in particular, the mode of presentation would be expected to depend for uniformity directly on the strengths of the interactions between the substituents I, A, K, B, at the end of the growing chain and those attached to the monomer molecule.

A small number of chain configurations, determined by *X*-ray- or electron-diffraction methods, have been recorded for polymers containing asymmetric carbon atoms.

Fuller (*Chem. Reviews*, **1940**, **26**, 164), from *X*-ray crystallographic analysis, has assigned to poly(vinyl chloride) a structure identical with (10) [or (11); isolated sections are identical].

From electron-diffraction patterns of multilayers of the polymers, Coumoulos (*Proc. Roy Soc.*, **1944**, *A*, **182**, 166) has deduced structures identical with (10) [or (11)] for poly-(methyl and ethyl acrylate), five poly(alkyl methacrylates), and for poly(vinyl acetate).

Poly(vinyl acetate) (which has not been obtained crystalline) yields on hydrolysis poly(vinyl alcohol), which crystallises well in fibre form. From the most recent *X*-ray crystallographic analysis Bunn (*Nature*, **1948**, **161**, 929) concludes that the hydroxyl groups are essentially randomly placed in left- and right-hand positions along the chain, and (personal communication) that regular sequences longer than 3 or 4 monomer units are rare. If hydrolysis proceeds by acyl–oxygen fission then the order in poly(vinyl alcohol) ought to be equal to that in poly(vinyl acetate). Coumoulos (above) has found the ordered structure (10) [or (11)] for the latter, and it is now suggested that the chain configuration is rendered irregular by the intervention of vicinal acetyl groups during hydrolysis, leading to alkyl–oxygen fission. The results of Winstein and his co-workers (summarised by Braude, *Ann. Reports*, **1949**, **46**, 122) show vicinal intervention to be probable during the hydrolysis of such a structure as poly(vinyl acetate). For example, if the intermediate



(XX)

(XX) is formed as shown, then further hydrolysis by acyl–oxygen fission leads to (overall) inversion if at C_γ, but to retention if at C_α, while bimolecular attack by hydroxyl ion leads to inversion if at C_α, but to retention if at C_γ.

If it be assumed that poly(vinyl chloride) and the acetate, and the above poly-acrylates and -methacrylates, are formed by *trans*-addition, then in each instance reaction has proceeded with the presentation, [I′], in which like groups are at the maximum distance apart.

The present conclusions are summarised as follows.

The configuration of a growing ethylenic-addition chain-molecule is governed by three factors: (*a*) *trans*-, alternatively *cis*-, addition; (*b*) the mode of presentation of the monomer to the chain end; (*c*) the steric configuration of the attack by the initiating radical or ion. The recorded steric evidence implies *trans*-addition for both ionic and free-radical mechanisms. The regular operation of factors (*a*), (*b*), (*c*), leads to the formation of a limited number of orderly chain-configurations. Mutual termination of chains may yield molecules of more complex diastereoisomeric types, but can also lead to highly symmetrical *meso*-structures.

Battersea Polytechnic, London, S.W.11. [*Received, March 11th*, 1955.]

Studies in the Synthesis of Cortisone. Part XII. Improvements in the Conversion of Sapogenins into Pregnan-20-ones.*

By A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, and A. G. Long.

[Reprint Order No. 6251.]

The conversion of steroidal sapogenins (I) into pregnan-20-ones (VI) by way of the ψ-sapogenins (II) is improved, particularly for 11-oxotigogenin and its esters (I*c*). In the first step furost-22-ens are evidently formed as well as the desired ψ-sapogenins, but this difficulty and others are avoided by methods described.

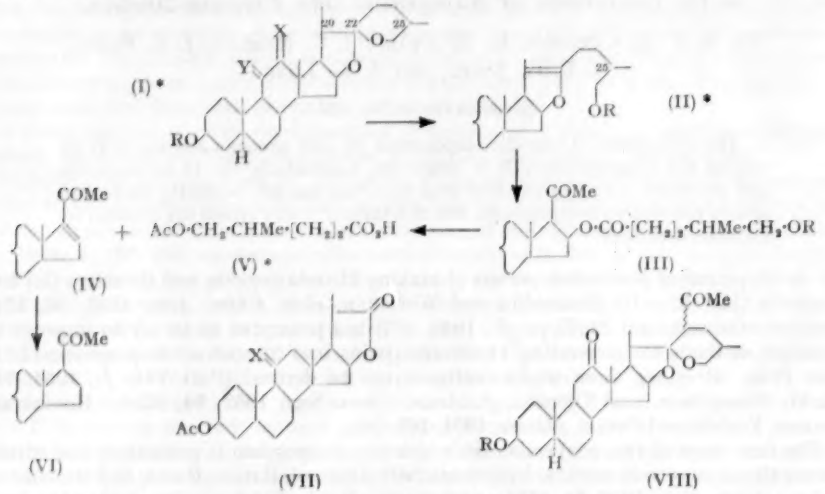
The development of practicable means of making 11-oxotigogenin and its esters (I*c*) from hecogenin (I*b*; R = H) (Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241; Cornforth, Osbond, and Phillipps, *J.*, 1954, 907) has prompted us to try to improve the published methods for converting 11-oxosapogenins into 3β-acetoxy-5α-pregnane-11 : 20-dione (VI*c*; R = Ac), from which cortisone can be derived (Part VII, *J.*, 1954, 747; Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615; Rosenkranz, Djerassi, Yashin, and Pataki, *Nature*, 1951, **168**, 28).

The first stage of this conversion (in which the ψ-sapogenin is generated) has entailed heating the sapogenin in acetic anhydride at 200° (Djerassi, Batres, Romo, and Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 3634; Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *ibid.*, 1953, **75**, 3477); as the reaction mixture corrodes stainless steel, special apparatus is needed for work on a large scale. Marker and Rohrmann (*ibid.*, 1940, **62**, 518; cf. Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 578; Shoppee and Shoppee, "Chemistry of Carbon Compounds," edited by Rodd, Elsevier, Amsterdam, 1953, Vol. II*B*, p. 1035), who devised this method for the degradation, claimed good yields when it was applied to simple sapogenins of the normal and *iso*-series, and they and later workers also used refluxing *n*-butyric anhydride at ordinary pressures (Mueller, Stobaugh, and Winniford, *J. Amer. Chem. Soc.*, 1953, **75**, 4888; Uhle, *ibid.*, 1954, **76**, 4245). We found octanoic anhydride (b. p. 285°) more effective (experiments with acetic anhydride in sealed tubes succeeded best at >200°). At these temperatures fatty acids generate small proportions of their anhydrides (and therefore presumably of the active acetylium ions) (Davidson and Newman, *ibid.*, 1952, **74**, 1515); accordingly we found acetic acid nearly as efficient as its anhydride in the degradation of 11-oxotigogenin acetate (I*c*; R = Ac) at 270°, although Marker and Rohrmann (*loc. cit.*) had dismissed it as ineffective at 200° on sarsasapogenin acetate (I*e*; R = Ac). Further, in *n*-octanoic acid (b. p. 237°), the desired change took less than 2 hr., and 3β : 26-dihydroxy-5α : 25*D*-furost-20-en-11-one (II*c*; R = H) was obtained, after hydrolysis, in 85—90% yield. The water generated in this conversion can be removed by distillation or, better, by addition of an acid anhydride (*e.g.*, acetic or octanoic anhydride). This method was successful also for the degradation to their ψ-isomers of the genins (I*a*; I*d*; I*e*; I*f*; and I*b*; R = H), and can be adapted readily to a large scale. Benzoic acid and aliphatic dicarboxylic acids are less suitable reagents than the simple fatty acids.

Gould, Staeudle, and Hershberg (*ibid.*, 1952, **74**, 3685; Rust, U.S.P. 2,623,053) have also studied alternatives to the method invented by Marker and Rohrmann. Although refluxing acetic anhydride does not perceptibly promote the required breakdown, Gould *et al.* found that Friedel–Crafts catalysts converted diosgenin acetate (I*f*; R = Ac) in refluxing acetic anhydride into ψ-diosgenin diacetate (II*f*; R = Ac). Using 11-oxotigogenin acetate (I*c*; R = Ac), we tried milder catalysts, *e.g.* zinc acetate, with slightly better success, and with trichloroacetic acid achieved the conversion in refluxing acetic acid containing only enough of the anhydride to esterify the hydroxyl groups. For

* Part XI, *J.*, 1955, 2017.

reasons discussed below unwanted changes militate against high yields of the ψ-compounds by these methods.



Series (*a*) X = Y = H_2; (*b*) X = O, Y = H_2; (*c*) X = H_2, Y = O; (*d*) 5β-H, X = Y = H_2; (*e*) 5β-H, X = Y = H_2; normal sapogenin; * (*f*) Δ^5, X = Y = H_2.

* The formulæ are not intended to specify the configurations at $C_{(20)}$, $C_{(22)}$, and $C_{(25)}$ in (I) or (VIII), at $C_{(25)}$ in (II), at $C_{(22)}$ in (VII), or at the asymmetric centre in (V). The stereochemistry of these sapogenins at $C_{(25)}$ and of the acid (V) can now be deduced (see Callow *et al.*, *J.*, 1955, 1966). Except for (I*e*) and (II*e*) all the spirostan and furosten derivatives described in this paper have the 25*D*-configuration.

Dauben, Eastham, Micheli, Takemura, Mandell, and Chemerda (*J. Amer. Chem. Soc.*, 1953, **75**, 3255) noticed degradation of the *spiro*ketal side chain of a sapogenin in pyridine–acetyl chloride, and Dauben and Fonken (*ibid.*, 1954, **76**, 4618) found acetic anhydride and pyridine hydrochloride to be efficient with diosgenin acetate (I*f*; R = Ac). Conditions of the former type gave poor results with our compounds; we have not tried the latter.

The pure ψ-sapogenins behave as expected of furost-20-ens: they give brown or yellow colours with tetranitromethane, and their cyclic vinyl ether chromophore endows them with an absorption maximum at about 216 mμ. Dihydrofurans with the >C=CH·O– chromophore have maxima at about 211 mμ (Eglinton, Jones, and Whiting, *J.*, 1952, 2873); therefore the shift of about 5 mμ (denoting the further alkyl substituent in the ψ-sapogenins on the carbon atoms joined by the double bond) resembles cognate effects in the absorption of conjugated dienes and $\alpha\beta$-unsaturated ketones (cf. Fieser and Fieser, *op. cit.*, p. 184). In their infrared absorption the ψ-sapogenins show a C=C stretching band at about 1690 cm.$^{-1}$ (Hayden, Smeltzer, and Scheer, *Analyt. Chem.*, 1954, **26**, 550), whereas other cyclic vinyl ethers show a maximum between 1600 and 1680 cm.$^{-1}$, and the nearest analogue to the furost-20-en structure, 2 : 3-dihydro-5-methylfuran at *ca.* 1675 cm.$^{-1}$ (Bader, *Helv. Chim. Acta*, 1953, **36**, 215; Rosenkranz and Gut, *ibid.*, p. 1000; Meakins, *J.*, 1953, 4170; Barr and Rose, *J.*, 1954, 3766). Other peaks at about 960 and 1025 cm.$^{-1}$ in the absorption spectra of the ψ-sapogenins are possibly due to C–O stretching vibrations, for similar maxima appear in the spectra of dihydrosapogenins and of many derivatives of tetrahydrofuran and tetrahydropyran (cf., *e.g.*, Burket and Badger, *J. Amer. Chem. Soc.*, 1950, **72**, 4397; Barker, Bourne, Stephens, and Whiffen, *J.*, 1954, 171, 3468, 4211; Callow, Dickson, Elks, Evans, James, Long, Oughton, and Page, *J.*, 1955, 1966; Meakins, *loc. cit.*).

The desired degradation of the sapogenins is continued by the opening of ring E in the ψ-sapogenin diesters (II). Of the oxidising agents suggested for this purpose (Marker and Rohrmann, *loc. cit.*; Marker, Jones, *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 2532; 1942,

64, 468; Mueller *et al.*, *loc. cit.*) we found chromic acid in acetic acid the best. The resulting 16β-acyloxy-20-oxo-steroid (III) cannot be easily purified, and is generally best used crude for the next stage. We chose acetic acid as agent for the elimination of the 16-acyloxy-substituent, after poor results with the acids and bases suggested by other workers (*e.g.*, Marker, Turner, Wagner, Ulshafer, Crooks, and Wittle, *ibid.*, 1941, **63**, 774, 779; Djerassi *et al.*, *loc. cit.*; Chamberlin *et al.*, *loc. cit.*), and in this way avoided hydrolysis of the 3β-acetate and addition of nucleophilic groups to the 16 : 17-double bond (Fukushima and Gallagher, *ibid.*, 1950, **72**, 2306), which are probable faults in the other methods. We were able to overcome such difficulties in other ways: thus, although elimination in the ester (IIIc) was almost imperceptible in refluxing solutions in benzene, the addition of an acidic earth such as silica promoted it; an anion-exchange resin or alumina also promoted it, even in the cold (cf. Gould *et al.*, *loc. cit.*; Mueller *et al.*, *loc. cit.*).

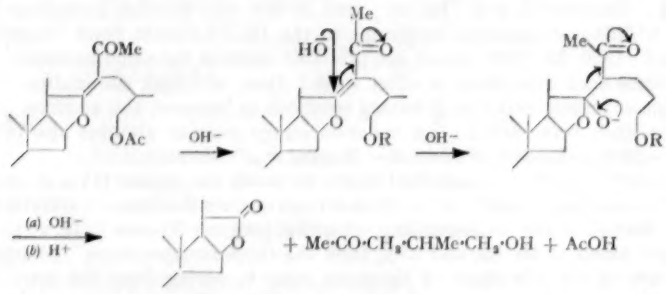
By the preferred methods mentioned above we made the enones (IV*a*, *c*, and *b*; R = Ac) from the genins (I*a*, *c*, and *b*; R = H) or certain of their 3-esters. Catalytic hydrogenation readily furnished the corresponding saturated pregnan-20-ones (VI*a*, *c*, and *b*; R = Ac) in average yields of 40, 65, and 55% from the three *iso*sapogenins. Shortcomings in the degradation of the side-chain of tigogenin seem to spring from the intractability of ψ-tigogenin (II*a*; R = H), for we made the ketone (VI*a*; R = Ac) in about the same yield from the hecogenin (I*b*; R = H) by converting the latter into ψ-hecogenin (II*b*; R = H), reducing this by the Wolff–Kishner method to ψ-tigogenin (II*a*; R = H) and then completing the degradation in the ordinary way.

In an appraisal of the effects of catalysts in refluxing acetic anhydride on the conversion of diosgenin (I*f*; R = H) into its ψ-isomer (II*f*; R = H) Gould *et al.* (*loc. cit.*) attributed some of their loss in yield to the formation of two by-products, namely, the Δ^{22}-isomer of the latter steroid, and a substance that they took to be an α-diketone, owing to its $\lambda_{max.}$ at 275 mμ, although they did not explain the origin of this chromophore. We agree that the furost-22-endiols may accompany the desired ψ-sapogenins if the initial ring cleavage is inadequately controlled. They are manifested by a trend of the optical rotation to the negative side. Moreover, ψ-sapogenin diesters contaminated with these isomers consume more oxidant than is required for rupture of a ditertiary double bond in ring E, and γ-lactones then accompany the desired 16-oxo-steroids in the products. We have been unable to isolate a pure specimen of a furost-22-en, but have segregated and identified a little of the lactone (VII; X = O, 5α-H) after oxidising the product from an experiment carried out with cold acetic anhydride containing phosphoric acid as catalyst. Like the pure ψ-sapogenin diacetates (II), 11-oxo*cyclo*-ψ-tigogenin acetate (11-oxo*ana*tigogenin acetate) afforded on oxidation hardly perceptible quantities of lactone. In acid solution the *cyclo*-ψ-compound would generate the isomeric 3β-acetoxyfurost-20-en-26-ol, in which form it becomes oxidisable (cf. Wall, Eddy, and Serota, *J. Amer. Chem. Soc.*, 1954, **76**, 2849; Callow *et al.*, *loc. cit.*).

We also noticed among our products substances with $\lambda_{max.}$ *ca.* 275 mμ, but we think that these contain not an α-diketone, but the chromophore $-C_{(22)}(OR)=C_{(23)}(COMe)-$ (cf. Attenburrow, Elks, Elliott, Hems, Harris, and Brodrick, *J.*, 1945, 571; Meek, Turnbull, and Wilson, *J.*, 1953, 2891; Szmuszkovicz, *J. Org. Chem.*, 1954, **19**, 1424; Gillam and Stern, "Electronic Absorption Spectroscopy," Arnold Ltd., London, 1954, p. 98), arising by *C*-acylation of the furost-22-en (cf. Henne and Tedder, *J.*, 1953, 3628; Burton and Praill, *Chem. and Ind.*, 1954, 75). After treating hecogenin acetate (I*b*; R = Ac) with perchloric acid in acetic anhydride at room temperature, we isolated yet another type of compound, which behaved as a *C*-acetylsapogenin, probably 23ξ-acetylhecogenin (cf. Marker, Turner, Shabica, and Ulshafer, *J. Amer. Chem. Soc.*, 1941, **63**, 1032; Mueller, Norton, Stobaugh, Tsai, and Winniford, *ibid.*, 1953, **75**, 4892). Its infrared absorption between 800 and 1100 cm.$^{-1}$ befits a sapogenin of this type rather than an *iso*sapogenin carrying the substituent in a position remote from rings E and F (Dickson and Page, *J.*, 1955, 447). It is possibly generated by cyclisation of a 23-acetylfurosten of the type just discussed.

23-Acetylfurost-22-ens are probably decomposed in alkali, owing to influences like those that determine the instability in such conditions of γ-pyrones ("Organic Chemistry," edited by Gilman, Wiley and Sons, Inc., New York, 1953, p. 824). This observation

helps to explain the generation of the γ-lactone (VII; X = H_2, 5β-H) as well as ψ-sarsasapogenin (II*e*; R = H) when sarsasapogenin acetate (I*e*; R = Ac) was degraded in acetic anhydride at 200°, and, after hydrolysis, the alkali-soluble part acidified (Marker and Rohrmann, *loc. cit.*), since it now seems reasonable that the annexed changes could lead to this result:



The possibility of side reactions originating in the furost-22-ens stresses the importance of control in the first stage of the degradations discussed in this paper.

Experimental

Unless stated otherwise, solutions as follows were used for measurements of the physical constants of the compounds described herein: in CS_2 and EtOH for infrared and ultraviolet spectra respectively, and in $CHCl_3$ for optical rotation. The apparatus used for obtaining the infrared spectra has been described elsewhere (Dickson, Page, and Rogers, *loc. cit.*). Owing to overlapping absorption by CS_2 the C=C stretching band for αβ-unsaturated ketones could be descried only in the spectra of CCl_4 solutions. Absorption bands were usually assigned by reference to Jones and Dobriner (*Vitamins and Hormones*, **1949**, **7**, 293) and Jones and Herling (*J. Org. Chem.*, **1954**, **19**, 1252) for the infrared, and Dorfman (*Chem. Reviews*, **1953**, **53**, 47) for the ultraviolet, region.

We used a Kofler m. p. apparatus.

n-Octanoic Anhydride.—*n*-Octanoic acid (**317** ml.) and acetic anhydride (**275** ml.) were refluxed for **18** hr. Distillation through a **6**-in. Vigreux column under a reduced pressure of anhydrous nitrogen gave the pure anhydride (**180** g., **71**%), b. p. **183**—**186°**/**16** mm., **280°**/**760** mm., m. p. **−0·5°**, n_D^{15} **1·4405**, $\nu_{max.}$ **1818** and **1752** cm.$^{-1}$ (acid anhydride) [Found: equiv. (by hydrolysis), **137·5**. Calc. for $C_{16}H_{30}O_3$: equiv., **135**]. Krafft and Rosiny (*Ber.*, **1900**, **33**, 3576), Autenrieth (*Ber.*, **1901**, **34**, **183**), and Holde and Genter (*Ber.*, **1925**, **58**, 1422) record b. p. **186°**/**15** mm., **280**—**285°**/**760** mm., m. p. **−1°**, $n_D^{17.5}$ **1·4358**.

Use of Anhydrides in the Conversion of **11**-*Oxotigogenin Acetate* (I*c*; R = Ac) *into* **11**-*Oxo*-ψ-*tigogenin* (II*c*; R = H).—The ψ-sapogenin was isolated as described below. Acetic anhydride at **200°**, used as described by Chamberlin *et al.* (*loc. cit.*) and Djerassi *et al.* (*loc. cit.*), gave the ψ-compound (II*c*; R = H) in **45**—**50**% yield. When the mixture was heated to **270°** (in **105** min.) and cooled immediately (**25**—**30** min.) the yield was raised to **71**%. Use of only a theoretical quantity of the anhydride and dilution with acetic acid (**0·5**—**5** vol.) gave a **52**% yield; when light petroleum (b. p. **118**—**122°**; critical temp. **>300°**; free from aromatic hydrocarbons) was used as diluent the yield was **68**%. Pure acetic anhydride becomes black in these circumstances, but the colour could be removed from the crude product (as its ester) by filtration of its ethereal solution through alumina.

When **11**-oxotigogenin acetate (I*c*; R = Ac) (**1** g.) was treated with refluxing *n*-octanoic anhydride (**4** ml.) or succinic anhydride (**4** g.) at ordinary pressure, a change occurred that finished in **30** or **7** min. respectively (assessed polarimetrically). **11**-Oxo-ψ-tigogenin (II*c*; R = H) was obtained therefrom in a yield of **58** or **82**%.

Use of Acids.—**11**-Oxotigogenin acetate (I*c*; R = Ac) was treated with refluxing acids (**2**—**5** vol.) and the products were worked up as described below. Except for the experiment with acetic acid these reactions were done at ordinary pressure, and the course of the conversion was studied polarimetrically, the water formed during the reaction being distilled off. The acid used, temperature and time of reaction, and yield of **11**-oxo-ψ-tigogenin (II*c*; R = H)

were: acetic, 270°, 105 min. (see above), 35%; *n*-hexanoic, 205°, 6 hr., 81%; *iso*hexanoic, 207°, 6 hr., 79%; *n*-octanoic, 237°, 2 hr., 83%; decanoic, 268°, 0·5 hr., 78%; myristic, 310°, 0·5 hr., 66%; oleic, 270°, 1 hr., 67%.

Phenylacetic, benzoic, and adipic acid furnished impure products in low yield.

Similar experiments, in which enough of the anhydride of the acid was added to take up the water produced, gave the following results: *n*-butyric acid, 169°, 24 hr., 80%; *n*-octanoic acid, 247°, 2 hr., 92%. During these times the rotations of the solutions had reached their maxima; on further refluxing, the rotation decreased, for reasons mentioned in the introduction.

For preparation of ψ-sapogenins the following was typical. 11-Oxotigogenin acetate (I*c*; R = Ac) (10 g.) was heated for 2 hr. in refluxing *n*-octanoic acid (13·2 ml.) containing *n*-octanoic anhydride (6·8 ml.) or acetic anhydride (5 ml.). In the latter instance the low-boiling fractions were distilled off until the temperature reached 240°, and the refluxing continued for 2 hr. thereafter. If octanoic acid is used without the anhydrides the result is as good, but the initial azeotropic removal of the water causes uneven boiling. The reaction mixture was cooled and extracted with ether or benzene. This extract was washed with 2N-sodium hydroxide and then with water. Evaporation of the organic phase left a gum that was hydrolysed in 0·5 hr. in refluxing methanol (100 ml.) containing potassium hydroxide (5 g.); addition of hot water then precipitated a white solid that was washed with plenty of water containing a little pyridine or alkali. The product (8·59 g., 94%) had m. p. 181—189°, $[\alpha]_D^{21}$ +74° (*c*, 1·0), and was suitable for most purposes. Crystallisation from methanol afforded an analytical specimen of 11-*oxo*-ψ-*tigogenin* (II*c*; R = H) (see below). In this manner the alcohol (I*c*; R = H) and benzoate (I*c*; R = Bz) were similarly converted into the foregoing ψ-compound. The yields of ψ-sapogenins when other sapogenins were similarly treated were: tigogenin acetate (I*a*; R = Ac) 98%; hecogenin acetate (I*b*; R = Ac) 92%; smilagenin (I*d*; R = H) 86%; sarsasapogenin acetate (I*e*; R = Ac) 27%, and diosgenin (I*f*; R = H) 87%. The properties of the products appear below. The 3 : 26-diacetates were obtained nearly quantitatively (except for ψ-tigogenin diacetate, which arose in *ca.* 60% yield) in 20—30 min. by acetylation of the ψ-sapogenins with acetic anhydride and pyridine (equal vols.) on the steam-bath.

(i) ψ-Tigogenin (II*a*; R = H), plates or needles (from methanol), m. p. 179—189°, $[\alpha]_D^{20}$ +24° (*c*, 0·47), $\lambda_{max.}$ 214 mμ (ε 5900), $\nu_{max.}$ see Dickson, Page, and Rogers, *J.*, 1955, 443 (Found: C, 77·9; H, 10·5. Calc. for $C_{27}H_{44}O_3$: C, 77·8; H, 10·65%). Marker and Rohrmann (*J. Amer. Chem. Soc.*, 1940, **62**, 898) give m. p. 193—196°. 3 : 26-Diacetate (II*a*; R = Ac), plates (from methanol), m. p. 68—70°, $[\alpha]_D^{20}$ +3·5° (*c*, 1·0), $\nu_{max.}$ 1735 and 1238 (acetate), and 1690 cm.$^{-1}$ (vinyl ether) (Found: C, 74·7; H, 9·7. Calc. for $C_{31}H_{48}O_5$: C, 74·4; H, 9·7%). Rosenkranz, Djerassi, Nussbaum, and Sandoval (*J. Org. Chem.*, 1952, **17**, 426) give m. p. 70—72°, $[\alpha]_D^{20}$ +7°.

(ii) ψ-Hecogenin (II*b*; R = H), plates (from aqueous acetone), m. p. 190—191°, $[\alpha]_D^{20}$ +103° (*c*, 1·5), +96° (*c*, 1 in dioxan), $\lambda_{max.}$ 213 mμ (ε 6400), $\nu_{max.}$ (Nujol) 3320 (hydroxyl), 1706 (ketone) and 1688 cm.$^{-1}$ (vinyl ether) (Found: C, 75·5; H, 10·0. Calc. for $C_{27}H_{42}O_4$: C, 75·3; H, 9·8%). Mueller, Stobaugh, and Winniford (*loc. cit.*) give m. p. 186—188°, $[\alpha]_D^{20}$ +84° (in dioxan). 3 : 26-Diacetate (II*b*; R = Ac), plates (from methanol), m. p. 92·5—94°, $[\alpha]_D^{20}$ +74° (*c*, 1·8), $\nu_{max.}$ 1738 and 1238 (acetate), 1710 (ketone), and 1688 cm.$^{-1}$ (vinyl ether) (Found: C, 72·55; H, 9·0. Calc. for $C_{31}H_{46}O_6$: C, 72·35; H, 9·0%). Mueller, Stobaugh, and Winniford (*loc. cit.*) give m. p. 92—94°, $[\alpha]_D^{20}$ +69° (dioxan).

(iii) 11-*Oxo*-ψ-*tigogenin* (II*c*; R = H), prisms (from methanol) or needles (from acetone), m. p. 194—196°, $[\alpha]_D^{20}$ +76° (*c*, 2), $\lambda_{max.}$ 215 mμ (ε 4950), $\nu_{max.}$ see Dickson, Page, and Rogers (*loc. cit.*) (Found: C, 75·0; H, 9·7. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%). 3 : 26-*Diacetate* (II*c*; R = Ac), m. p. 75—78°, $[\alpha]_D^{23}$ +45° (*c*, 1·23), $\lambda_{max.}$ 218 mμ (ε 5150), $\nu_{max.}$ 1732 and 1240 (acetate), 1708 (ketone), and 1690 cm.$^{-1}$ (vinyl ether) (Found: C, 72·4; H, 9·0. $C_{31}H_{46}O_6$ requires C, 72·35; H, 9·0%).

(iv) ψ-Smilagenin (II*d*; R = H) (from aqueous methanol), m. p. 158—161°, $[\alpha]_D^{23}$ +24° (*c*, 0·98), $\nu_{max.}$ (Nujol) 3300 (hydroxyl) and 1690 cm.$^{-1}$ (vinyl ether). Scheer, Kostic, and Mosettig (*J. Amer. Chem. Soc.*, 1953, **75**, 4871) give m. p. 158—161°, $[\alpha]_D^{20}$ +24°.

(v) ψ-Sarsasapogenin (II*e*; R = H) (from methanol), m. p. 165—168°, $[\alpha]_D^{24}$ +12° (*c*, 0·73), $\lambda_{max.}$ 215 mμ (ε 6050), $\nu_{max.}$ (Nujol) 3300 (hydroxyl) and 1688 cm.$^{-1}$ (vinyl ether). Scheer *et al.* (*loc. cit.*) give m. p. 167—169°, $[\alpha]_D^{20}$ +12°.

(vi) ψ-Diosgenin (II*f*; R = H) (from aqueous methanol), m. p. 157—163°, then 174—177°, $[\alpha]_D^{18}$ −36° (*c*, 1·7), $\lambda_{max.}$ 202 mμ (ε 9200) and 217 mμ (ε 6100), $\nu_{max.}$ 3300 (hydroxyl) and 1690 cm.$^{-1}$ (vinyl ether) (Found: C, 78·1; H, 10·4. Calc. for $C_{27}H_{42}O_3$: C, 78·2; H, 10·2%). Ziegler, Rosen, and Shabica (*ibid.*, 1954, **76**, 3865) give m. p. 165—168°, $[\alpha]_D^{25}$ −39°, $\nu_{max.}$ 1693 cm.$^{-1}$

for this compound. Earlier workers reporting different properties had probably overlooked the ease of the cyclisation to compounds with a high negative rotation (Marker, Tsukamoto, and Turner, *ibid.*, 1940, **62**, 2525; Kaufman and Rosenkranz, *ibid.*, 1948, **70**, 3502; cf. Callow *et al.*, *loc. cit.*). **3 : 26-Diacetate** (II*f*; R = Ac) sublimed at 130—140°/10^{-5} mm. and crystallised from methanol as rhombs, m. p. 102—104°, $[\alpha]_D^{20}$ −39° (*c*, 1·01), $\lambda_{max.}$ 206 (ε 8860) and 215 mμ (ε 7010), $\nu_{max.}$ 1732 and 1240 (acetate) and 1690 $cm.^{-1}$ (vinyl ether) (Found : C, 74·8; H, 9·3. Calc. for $C_{31}H_{46}O_5$: C, 74·7; H, 9·3%). The ultraviolet maxima given by these two compounds at the shorter wavelengths are presumably due to the 5 : 6-double bond. Kaufman and Rosenkranz (*loc. cit.*) give m. p. 97—98°, $[\alpha]_D$ −31°, Gould *et al.* (*loc. cit.*) m. p. 98·5—100·5°, $[\alpha]_D$ −47°, and Dauben and Fonken (*loc. cit.*), m. p. 95—98°, $[\alpha]_D^{25}$ −48°.

All of these ψ-sapogenins and their diacetates gave brown or yellow colours with tetranitromethane in chloroform. Their conversions into *cyclo*-ψ-compounds and thence into the parent sapogenins are described elsewhere (Callow *et al.*, *loc. cit.*). Mother-liquors from the crystallisations and purifications of ψ-sapogenins could in this way be made to yield usefully recoverable material.

Preparation of ψ-Tigogenin (II*a*; R = H) *from ψ-Hecogenin* (II*b*; R = H).—A solution of ψ-hecogenin (10 g.) in diethylene glycol (100 ml.) containing sodium hydroxide (10 g.) and hydrazine hydrate (6 ml.) was heated to 145° for 1 hr. under reflux. The condenser was then removed and the mixture heated during 5 hr. up to 205°. The product was left to cool under oxygen-free nitrogen. Methanol (100 ml.) was added, and the solution poured into water (500 ml.) and then set aside overnight; the precipitated ψ-tigogenin (II*a*; R = H) (9·06 g.), m. p. 180—185°, had no infrared carbonyl absorption. Acetylation and crystallisation of the product therefrom yielded the diacetate (II*a*; R = Ac) (8·0 g., 64%), m. p. and mixed m. p. 67—70°, $[\alpha]_D^{20}$ +3° (*c*, 1·0).

3β-Acetoxy-16β-γ-acetoxymethylvaleroyloxy-5α-pregnane-11 : 20-dione (III*c*; R = Ac).—To a solution of **3β : 26-diacetoxy-5α : 25*D*-furost-20(22)-en-11-one** (11-oxo-ψ-tigogenin diacetate) (II*c*; R = Ac) (4·3 g.) in " AnalaR " acetic acid (30 ml.) was added 1·39*N*-chromium trioxide in 90% acetic acid (31·5 ml.; 30% excess). The temperature was kept below 30°, and after 1·5 hr. the excess of oxidant (corresponding approximately to the calculated excess) was destroyed with methanol or sodium metabisulphite. Extraction of this solution with benzene or ether (from which the water-soluble and acidic materials were then removed with aqueous sodium hydrogen carbonate) and subsequent evaporation gave a dry residue that could be used for the next stage. Crystallisation from ethanol yielded needles (3·44 g., 76%) of the 16β-ester (III*c*; R = Ac), m. p. 133—134°, $[\alpha]_D^{24}$ +38°. A specimen crystallised to analytical purity had m. p. 131—133°, $[\alpha]_D^{23}$ +35° (*c*, 1·04), $\nu_{max.}$ 1736, 1240 and 1162 (esters), and 1714 $cm.^{-1}$ (ketone) (Found : C, 68·2; H, 8·3. Calc. for $C_{31}H_{46}O_8$: C, 68·1; H, 8·5%). Djerassi, Batres, Romo, and Rosenkranz (*J. Amer. Chem. Soc.*, 1952, **74**, 3635) give m. p. 128—130°, $[\alpha]_D^{20}$ +47°.

The acetic acid used as solvent in the above experiments could be diluted with ethylene dichloride without spoiling the efficiency of the reaction. Slightly inferior yields were obtained when potassium dichromate in acetone and dilute sulphuric acid, hydrogen peroxide in acetic acid (Mueller, Stobaugh, and Winniford, *loc. cit.*), or potassium permanganate in acetic acid (Marker, Jones *et al.*, *locc. cit.*) were used for the oxidation. These statements were also confirmed by comparing the respective yields of the Δ^{16}-20-ketone (IV*c*; R = Ac) when the crude ester (III*c*; R = Ac) was used after each oxidation for the next stage.

3β-Acetoxy-16β-γ-acetoxymethylvaleroyloxy-5α-pregnan-20-one (III*a*; R = Ac).—This was made from ψ-tigogenin diacetate (II*a*; R = Ac) in 74% yield by oxidation in the above manner with chromic acid. It crystallised from methanol as plates, m. p. 99—100°, $[\alpha]_D^{20}$ +14° (*c*, 1·0), $\nu_{max.}$ 1736, 1238, and 1164 (esters), and 1715 $cm.^{-1}$ (ketone) (Found : C, 69·9; H, 8·9. Calc. for $C_{31}H_{48}O_7$: C, 69·9; H, 9·1%). Marker, Turner, Wagner, Ulshafer, Crooks, and Wittle (*J. Amer. Chem. Soc.*, 1941, **63**, 774) give m. p. 102—104°. It seemed to be necessary to use pure specimens of this compound for successful conversion into the Δ^{16}-20-keto-steroid (IV*a*; R = Ac).

3β-Acetoxy-5α-pregn-16-ene-11 : 20-dione (IV*c*; R = Ac).—(*a*) To the 16β-ester (III*c*; R = Ac) (0·25 g.) in benzene (2·5 ml.) and light petroleum (b. p. 40—60°; 7·5 ml.) was added alumina (Spence Grade H; 2·5 g.; cf. Mueller, Stobaugh, and Winniford, *loc. cit.*). The slurry was shaken or stirred at room temperature, for 2 hr., then filtered, and the alumina washed with ether–methylene chloride (1 : 1; *ca.* 50 ml.). Evaporation of the combined filtrate and eluate, and crystallisation of the residue from ether, gave the enone (IV*c*; R = Ac) (0·16 g., 94%), m. p. 178—181°, $[\alpha]_D^{14}$ +64° (*c*, 1·3), $\lambda_{max.}$ 235 mμ (ε 9150). Similar results were achieved when a solution of the ester (III*c*; R = Ac) in benzene containing silica (B.D.H. " pure precipitated ")

was refluxed for 5 hr., or when a benzene solution of the ester containing the anion-exchange resin A 3 (sold by Colborne Engineering Co. Ltd., London, W.3) was kept for 24 hr. at room temperature with occasional shaking. The product from the experiment with silica was washed with aqueous sodium hydrogen carbonate to remove acidic by-products.

(*b*) The 16β-ester (III*c*; R = Ac) (5 g.) was refluxed in glacial acetic acid (50 ml.) for 2 hr. The solvent was then removed *in vacuo*, and the residue dissolved in methylene chloride. Washing with sodium hydrogen carbonate solution and then several times with water, and evaporation of the dried ($MgSO_4$) lower phase left a residue that crystallised from ether as rods of the Δ^{16}-20-ketone (IV*c*; R = Ac) (3·2 g., 94%), m. p. 178—181°, $[\alpha]_D^{20}$ +64° (*c*, 1·0), $\lambda_{max.}$ 235 mμ (ε 9300). Recrystallisation from methanol gave an analytical specimen as rods, m. p. 182—184°, $[\alpha]_D^{20}$ +65° (*c*, 2), $\lambda_{max.}$ 235 mμ (ε 9150), $\nu_{max.}$ 1730 and 1288 (acetate), 1706 (ketone), 1670 and 1592 (αβ-unsaturated ketone), and 822 cm.$^{-1}$ (trisubstituted ethylene). The 1592-cm.$^{-1}$ peak could be discerned only in spectra of solutions in CCl_4 (Found: C, 74·25; H, 8·6. Calc. for $C_{23}H_{32}O_4$: C, 74·2; H, 8·7%). The properties of this material agree with those given by, *e.g.*, Djerassi *et al.* and Chamberlin *et al.* (*locc. cit.*). The use of sodium hydroxide in tetrahydrofuran (*idem*, *loc. cit.*), of potassium hydrogen carbonate in *tert.*-butanol (Mueller Stobaugh, and Winniford, *loc. cit.*) or of methanolic hydrogen chloride (Marker, Turner, *et al.*, *locc. cit.*) for the conversion of the ester (III*c*; R = Ac) into the foregoing Δ^{16}-ketone (IV*c*; R = Ac) resulted in poor yields.

Tigogenin acetate (I*a*; R = Ac), hecogenin acetate (I*b*; R = Ac), 11-oxotigogenin (I*c*; R = H), and the acetate (I*c*; R = Ac) and benzoate (I*c*; R = Bz) of the last-named were converted into the corresponding Δ^{16}-20-keto-steroids (IV) by the sequence (I) ⟶ (II) ⟶ (III) ⟶ (IV) + (V), without purification of the furostendiols or their acetates (II), or of the esters (III). A slightly increased uptake of oxidant (5—10%) was then observed in the oxidation of the furosten diesters, and the mother-liquors from the crystallisation of the Δ^{16}-keto-steroids contained a compound with $\nu_{max.}$ 1780 cm.$^{-1}$ (γ-lactone). We made the enones (IV*a*, *b*, and *c*; R = Ac) in this way from the three *iso*sapogenins and their esters. Analytical specimens were obtained, as follows.

(i) 3β-Acetoxy-5α-pregn-16-en-20-one (IV*a*; R = Ac), leaflets (from methanol), m. p. 166°, $[\alpha]_D^{20}$ +35° (*c*, 0·51), $\lambda_{max.}$ 239 mμ (ε 10,600), $\nu_{max.}$ 1735 and 1238 (acetate), 1668 (αβ-unsaturated carbonyl), and 816 cm.$^{-1}$ (trisubstituted ethylene) (Found: C, 77·05; H, 9·4. Calc. for $C_{23}H_{34}O_3$: C, 77·05; H, 9·55%). Plattner, Ruzicka, Heusser, and Angliker (*Helv. Chim. Acta*, 1947, **30**, 385) give m. p. 166—167°, $[\alpha]_D$ +42°, and Klyne, Schachter, and Marrian (*Biochem. J.*, 1948, **43**, 231) m. p. 165—167°, $[\alpha]_D$ +36·3°.

(ii) 3β-Acetoxy-5α-pregn-16-ene-12 : 20-dione (IV*b*; R = Ac), plates (from ether), m. p. 178—180°, $[\alpha]_D^{20}$ +128° (*c*, 2), $\lambda_{max.}$ 228 mμ (ε 10,100), $\nu_{max.}$ 1730 and 1240 (acetate), 1718 (ketone), 1678 (αβ-unsaturated ketone), and 824 cm.$^{-1}$ (trisubstituted ethylene). Mueller, Stobaugh, and Winniford (*loc. cit.*) give m. p. 179—181°, $[\alpha]_D^{25}$ +124° (in dioxan), $\lambda_{max.}$ 227·5 mμ (ε 8500) for this compound. On one occasion crystallisation of the above compound from methanol afforded material, m. p. 173—175°, $[\alpha]_D^{20}$ −11° (*c*, 2), $\lambda_{max.}$ 242 mμ ($E_{1\,cm.}^{1\%}$ 303), $\nu_{max.}$ at 3350 (hydroxyl), 1735 and 1240 (acetate), and 1654 cm.$^{-1}$ (αβ-unsaturated ketone). This result could not be repeated, even with methanol containing added traces of acid or alkali, anhydrous or containing a little water. Attempts to acetylate the hydroxyl group with cold pyridine and acetic anhydride decomposed the compound, and only the Δ^{16}-20-ketone (IV*b*; R = Ac) was isolated. We believe that a hemiketal group may have formed at the 12-position, inasmuch as peaks in the infrared absorption at 1185, 1148, 1120, 1075, and 1057 cm.$^{-1}$ might denote absorption of this type (Page, *J.*, 1955, 2017). The possibility that the novel compound is an aldol arising from interaction of the 12-keto-group with the activated 21-methyl (cf. Fieser and Fieser, *op. cit.*, p. 667; Arigoni, Riniker, and Jeger, *Helv. Chim. Acta*, 1954, **37**, 878) seems to be discredited by the position of the carbonyl absorption band, which is not appropriate for a cyclic ketone.

Conversion of 11-*Oxo*cyclo-*ψ-tigogenin Acetate into* 3β-*Acetoxy-5α-pregn*-16-*ene*-11 : 20-*dione* (IV*c*; R = Ac).—The 11-oxo*cyclo*-*ψ*-sapogenin (2 g.) (Callow *et al.*, *loc. cit.*) was dissolved in acetic acid (50 ml.) and oxidised with 1·39N-chromic oxide in 90% acetic acid (30·5 ml.). The solution was set aside for 3·5 hr. The excess of oxidant was removed by the addition of aqueous sodium metabisulphite, and the steroid extracted into benzene. Treatment with alumina as described heretofore yielded the pure Δ^{16}-20-oxo-steroid (IV*c*; R = Ac) (0·518 g., 33%), m. p. 180—182°, $[\alpha]_D^{21}$ +64° (*c*, 1·2), $\lambda_{max.}$ 235 mμ (ε 9200). The material in the mother-liquors contained no more than a trace of γ-lactone (on the basis of the infrared spectrum), but was contaminated with a neutral substance of low rotation and ultraviolet absorption.

Hydrogenation of the Foregoing Δ^{16}-20-*Keto-steroids*.—Each of the enones was hydrogenated

almost quantitatively with 5% palladised charcoal in ethyl acetate under hydrogen at atmospheric pressure and temperature. In this way we obtained the following 20-keto-steroids derived from tigogenin, hecogenin, and 11-oxotigogenin.

(i) 3β-Acetoxy-5α-pregnan-20-one (VI*a*; R = Ac), plates (from acetone), m. p. 144—145°, $[\alpha]_D^{20}$ +75° (*c*, 1·0), $\nu_{max.}$ 1732 and 1242 (acetate), 1706 (ketone), and 1356 cm.$^{-1}$ (methyl ketone) (Found: C, 76·5; H, 10·1. Calc. for $C_{23}H_{36}O_3$: C, 76·6; H, 10·1%). Barton and Cox (*J.*, 1948, 791) give m. p. 143·5—144·5°, $[\alpha]_D$ +77°.

(ii) 3β-Acetoxy-5α-pregnane-12 : 20-dione (VI*b*; R = Ac), crystals (from ethyl acetate), m. p. 188—190°, $[\alpha]_D^{20}$ +140° (*c*, 1·0), $\nu_{max.}$ 1738 and 1240 (acetate), and 1710 cm.$^{-1}$ (ketones). Mueller, Stobaugh, and Winniford (*loc. cit.*) give m. p. 189—190°, $[\alpha]_D$ +139° (in dioxan).

(iii) 3β-Acetoxy-5α-pregnane-11 : 20-dione (VI*c*; R = Ac), see next paragraph.

Physical Properties of 3β-*Acetoxy-5α-pregnane*-11 : 20-*dione* (VI*c*; R = Ac).—Crystallisation from aqueous methanol afforded needles, m. p. 127—128°, solidifying and remelting at 143—145°. Material fused at 130—135° and crystallised from aqueous methanol gave plates, m. p. 142—144°. Crystallisation of either form in the presence of the other gave mixed crystals. Each of the two forms had $[\alpha]_D^{20}$ +89° (*c*, 2), and their solutions gave identical infrared spectra (see Dickson, Page, and Rogers, *loc. cit.*) (Found: C, 73·8; H, 9·2. Calc. for $C_{23}H_{34}O_4$: C, 73·75; H, 9·2%). The ketone obtained from ergosterol (Cameron *et al.*, *loc. cit.*) behaved similarly. Djerassi *et al.* (*loc. cit.*) give m. p. 143—145°, $[\alpha]_D$ +87°, and Chamberlin *et al.* (*loc. cit.*), m. p. 124—127° (needles), 141—143° (plates), $[\alpha]_D$ +86°.

Hydrolysis of either form (1 g.) with potassium hydroxide (0·5 g.) for 0·5 hr. in refluxing methanol (10 ml.), and subsequent dilution with water yielded white needles (0·8 g.), m. p. 185—191°, $[\alpha]_D^{22}$ +106° (*c*, 0·6). Recrystallisation from ethyl acetate–*cyclo*hexane and acetone furnished needles, m. p. 192—196°, $[\alpha]_D^{22}$ +110° (*c*, 0·6), $\nu_{max.}$ (Nujol) at 3470 and 3400 (hydroxyl), 1698 (ketone) and 1352 cm.$^{-1}$ (methyl ketone), of 3β-hydroxy-5α-pregnane-11 : 20-dione (VI*c*; R = H) (Found: C, 76·2; H, 9·7. Calc. for $C_{21}H_{32}O_3$: C, 75·9; H, 9·7%). Cameron, Hunt, Oughton, Wilkinson, and Wilson (*J.*, 1953, 3864) give m. p. 188—190°, $[\alpha]_D$ +109°, and Stork, Romo, Rosenkranz, and Djerassi (*J. Amer. Chem. Soc.*, 1951, **73**, 3546) m. p. 192—194°, $[\alpha]_D$ +99°. By reacetylation it yielded the acetate (VI*c*; R = Ac), the form of which depended on the method of crystallisation.

It seems likely that catalytic hydrogenation occurs only on the " after " face of the molecule of the enone (VI*c*; R = Ac) (Shoppee and Shoppee, *op. cit.*, p. 901) and, as epimerism at $C_{(17)}$ is marked by large rotational differences (Fieser and Fieser, *op. cit.*, p. 390), the two forms cannot be 17-epimers and must be dimorphous (cf. Dickson, Page, and Rogers, *loc. cit.*).

3β-n-*Octanoyloxy-5α-pregn*-16-*ene*-11 : 20-*dione* (IV*c*; R = C_7H_{15}·CO).—11-Oxotigogenin (I*c*; R = H) (5 g.), *n*-octanoic anhydride (6·9 ml.) and acid (2 ml.) were refluxed together for 2 hr. The crude furosten diester was isolated without hydrolysis and then oxidised and treated with alumina as described above. The above 3-*octanoate* was obtained as a crystalline mass (4·76 g., 90%). Crystallised from light petroleum–ether it had m. p. 94—99°. The specimen for analysis separated from methanol as plates, m. p. 99—101°, $[\alpha]_D^{20}$ +51° (*c*, 0·9), $\lambda_{max.}$ 235 mμ (ε 9700), $\nu_{max.}$ 1728 and 1175 (ester), 1708 (ketone), 1672 (αβ-unsaturated ketone), and 821 cm.$^{-1}$ (trisubstituted ethylene) (Found: C, 76·1; H, 9·8. $C_{29}H_{44}O_4$ requires C, 76·3; H, 9·7%).

3β-n-*Octanoyloxy-5α-pregnane*-11 : 20-*dione* (VI*c*; R = C_7H_{15}·CO).—The foregoing Δ^{16}-20-ketone (3·3 g.) was hydrogenated as described above with the catalyst (0·7 g.) in ethyl acetate (70 ml.). Uptake of hydrogen being very slow, more catalyst (1·4 g.) was added, and the reduction was then completed in 1 hr. The steroidal product crystallised as rhombs (2·5 g., 75%), m. p. 40—50°, from methanol. Recrystallisation afforded the saturated 11 : 20-*dione* (1·79 g.), m. p. 55—60°, $[\alpha]_D^{20}$ +69° (*c*, 0·8), $\nu_{max.}$ 1725 and 1166 (ester), and 1707 cm.$^{-1}$ (ketone) (Found: C, 76·0; H, 9·95. $C_{29}H_{46}O_4$ requires C, 75·9; H, 10·1%).

Hydrolysis yielded the diketone (VI*c*; R = H), m. p. 185—190°, $[\alpha]_D^{20}$ +110° (*c*, 1·2), identified by mixed m. p. and infrared spectroscopy with a specimen described above.

Degradations in Refluxing Acetic Anhydride containing Catalysts.—11-Oxotigogenin acetate (I*c*; R = Ac) (5 g.) (which is not changed in refluxing acetic anhydride) was heated for 23 hr. in the refluxing anhydride (165 ml.) containing zinc acetate (2·5 g.). The product was filtered, and the filtrate extracted into ether, and washed therein with sodium hydrogen carbonate solution and water. Evaporation of the washed and dried ($MgSO_4$) ether phase left a gum that was oxidised with chromic oxide and treated with alumina in the usual manner. Isolation of the final product yielded the enone (IV*c*; R = Ac) (1·72 g., 45%), m. p. 173—179°, $[\alpha]_D^{20}$ +65° (*c*, 2), $\lambda_{max.}$ 235 mμ (ε 9300). After similar experiments in which concentrated hydrochloric acid (3 ml.) and dichloroacetic acid (16 g.) (severally) were used as catalysts, the enone (IV*c*;

R = Ac) was isolated in yields of 11 and 9%. When acetic acid with the theoretical amount of anhydride to combine with the hydroxyl groups was used as solvent, with trichloroacetic acid (2·25 g.) as catalyst, the yield was 36%. Aluminium chloride in acetic anhydride promoted a change in the sapogenin (assessed polarimetrically), but no Δ^{16}-20-ketosteroid could be obtained. A mixture of acetic anhydride and β-picoline failed to change the sapogenin. In the conditions described by Dauben *et al.* (*loc. cit.*, 1953) excessive darkening occurred.

After the formation of the furosten diacetate (II*c*; R = Ac) in the successful catalysed conversions another change set in, marked by a trend in the rotation to the negative side. Thus, cooled aliquot parts of a refluxing solution of the sapogenin (I*c*; R = Ac) in acetic anhydride made N with respect to dichloroacetic acid had $[\alpha]_D$ +40° and −20° after 1·5 hr. and 6 hr. respectively, and solutions of the *pseudo*-sapogenin diacetate (II*c*; R = Ac) behaved similarly. The significance of these changes is manifest in the results of catalysed conversions taking place in cool acetic anhydride (see below).

Tigogenin acetate (I*a*; R = Ac) was more stable in conditions of the foregoing type: for instance, it was recovered after 23 hours' refluxing with acetic anhydride containing zinc acetate in suspension.

Lactone (VII; X = O, 5α-H) *of* 3β-*Acetoxy*-16β-*hydroxy*-11-*oxobisnor*-5α-*cholanic Acid*.—11-Oxotigogenin acetate (I*c*; R = Ac) (5 g.) was treated with acetic acid (125 ml.) and acetic anhydride (125 ml.) containing "AnalaR" phosphoric acid (2·7 ml.; *d*, 1·74; final concn. 0·11M), and kept in the dark for 40 days (the rotation was then constant). The solution was extracted with chloroform, washed with water, and evaporated. The residual gum, dissolved in acetic acid (60 ml.), was oxidised with 1·39N-chromic acid in 90% acetic acid (40 ml.) for 2·5 hr.; methanol was then added, and the solvents were distilled off *in vacuo*. Extraction of the steroid with ether (with salting of the aqueous phase), washing with water, and evaporation of the dried ($MgSO_4$) ether phase left a residue that gave a white solid when triturated with ether. Crystallisation from ethanol yielded the *lactone* (VII; X = O, 5α-H) (0·150 g., 3%), m. p. 250—262°. An analytical specimen was obtained by subliming this product at 220°/10^{-4} mm. and subsequently crystallising the sublimate from ethanol as laminæ, m. p. 266—268°, $[\alpha]_D^{21}$ −23° (*c*, 1·2), $\nu_{max.}$ (in $CHBr_3$) 1762 (γ-lactone), 1710 and 1250 (acetate), and 1710 cm.$^{-1}$ (ketone) (Found: C, 71·5; H, 8·3. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%). A solution of this lactone in CS_2 gave lactonic carbonyl absorption at $\nu_{max.}$ 1780 cm.$^{-1}$, as did the lactone of the 16β-hydroxybisnor-5α-cholanic acid (VII; X = H_2, 5α-H) (derived from tigogenin) and its 5β-isomer (VII; X = H_2, 5β-H) (derived from sarsasapogenin and smilagenin) (Tschesche and Hagedorn, *Ber.*, 1935, **68**, 1412; Farmer and Kon, *J.*, 1937, 414).

23ξ-*Acetylhecogenin* (VIII; R = H).—Hecogenin acetate (I*b*; R = Ac) (10 g.) in alcohol-free chloroform (100 ml.) was treated with 60% perchloric acid (2 ml.) in acetic anhydride (20 ml.). The solution became warm and reddened. It was left for 20 min., and washed with aqueous sodium hydroxide and water. The dried ($MgSO_4$) organic phase, on evaporation, left a yellow glass (11·32 g.) that was hydrolysed in 2·5 hr. in refluxing 10% ethanolic sodium hydroxide (100 ml.). Precipitation of the product with water and subsequent crystallisation from aqueous ethanol (charcoal) yielded 23ξ-*acetylhecogenin* (VIII; R = H) (2·04 g., 20%), m. p. 243—246°. It crystallised from acetonitrile as fine needles, m. p. 247—251°, $[\alpha]_D^{20}$ −14° (*c*, 0·42), $\nu_{Nax.}$ (Nujol) 3580 (hydroxyl), 1708 (ketone), and 1352 cm.$^{-1}$ (methyl ketone), and a pattern of bands (see below) that distinguish this compound from an ordinary *iso*sapogenin (Found: C, 73·2; H, 9·3. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%). This compound gave an immediate positive test for a ketone with 2:4-dinitrophenylhydrazine (cf. Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof, *J. Amer. Chem. Soc.*, 1947, **69**, 2167) and for a methyl ketone with sodium nitroprusside (Feigl, "Qualitative Analyse mit Hilfe von Tüpfelreaktionen," Akademische Verlagsgesellschaft m.b.H., Leipzig, 1935, p. 375). 3β-*Acetoxy*-23ξ-*acetylhecogenin* (VIII; R = Ac), made from the above compound (0·5 g.) with pyridine (2·5 ml.) and acetic anhydride (2·5 ml.) in 1 hr. at 90°, crystallises as fluffy needles (0·45 g.) (from aqueous acetone), m. p. 213—216°, $[\alpha]_D^{20}$ −22° (*c*, 1·06), $\nu_{max.}$ 1732 and 1240 (acetate), 1708 (ketone), 1352 (methyl ketone), 1010, 955, 935, and 900 cm.$^{-1}$ (23-substituted sapogenin; cf. Dickson and Page, *loc. cit.*) (the intensity of the peak at 1708 cm.$^{-1}$ suggested the presence of two carbonyl groups) (Found: C, 72·9; H, 8·9. $C_{31}H_{46}O_6$ requires C, 72·3; H, 9·0%).

Treatment of hecogenin acetate (I*b*; R = Ac) or 11-oxotigogenin acetate (I*c*; R = Ac) at 0° or room temperature with *ca.* 0·1N-perchloric acid in acetic anhydride for 1 hr. made the rotation negative, its magnitude depending markedly on the dilution and diluent. After the addition of potassium acetate, water precipitated the two products with indefinite m. p.s,

$[\alpha]_D^{20}$ +7·5° (*c*, 1·0), $\lambda_{max.}$ 274·5 mμ ($E_{1cm.}^{1\%}$ 174), $\nu_{max.}$ 1735 and 1238 (acetate), 1710 (ketone) and (weak) 1666 cm.$^{-1}$ (αβ-unsaturated ketone), and $[\alpha]_D^{26}$ +19° (*c*, 1·0), $\lambda_{max.}$ 275 mμ ($E_{1cm.}^{1\%}$ 117), $\nu_{max.}$ 1735 and 1240 (acetate), 1709 (ketone), and (weak) 1671 cm.$^{-1}$ (αβ-unsaturated ketone). Neither substance could be got pure. Each presumably contains the 23-acetylfurost-22-en. The second substance, derived from the 11-ketone (I*c*; R = Ac), was not appreciably changed by attempted oxidation with chromic oxide in acetic acid and the usual working up with alumina (see above); it gave a 2 : 4-dinitrophenylhydrazone, $\lambda_{max.}$ (in $CHCl_3$) 372 mμ ($E_{1cm.}^{1\%}$ 293).

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Aromatic Azo-compounds. Part VII. The Synthesis and Absorption Spectra of Some Azoquinolines.*

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Five azoquinolines have been synthesised for comparison with the carcinogenic 2 : 2′-azonaphthalene. The absorption spectra have been compared with those of the azonaphthalenes and phenylazonaphthalenes.

2 : 2′-AZONAPHTHALENE is of interest in cancer research as it produces liver tumours in mice but is inactive or only very weakly active in rats (Cook *et al.*, *Amer. J. Cancer*, 1940, **40**, 62; Badger, Lewis, and Reid, *Nature*, 1954, **173**, 313), thus contrasting with 4-dimethylaminoazobenzene which is active in rats but relatively inactive in mice. Synthesis of a number of azoquinolines was accordingly undertaken.

6 : 6′-Azoquinoline was obtained by Knueppel (*Annalen*, 1900, **310**, 75) in small yield as a by-product in the reduction of 6-nitro- to 6-amino-quinoline by iron powder and calcium chloride. Our attempts to improve the yield by using other methods of reduction failed, so an alternative synthesis was sought, especially as Macey and Simpson (*J.*, 1952, 2602) have suggested that Knueppel was mistaken in the identity of his compound.

Azonaphthalenes have been synthesised by sulphite reduction of diazotised naphthylamines (Cohen and Oesper, *Ind. Eng. Chem. Anal.*, 1936, **8**, 306). This method, applied to 6-aminoquinoline, gave 6 : 6′-azoquinoline in 80% yield. The product was identical with that prepared by Knueppel's method. 7 : 7′- and 5 : 5′-Azoquinoline were similarly prepared. The method, however, failed with the diazonium derivatives of 3- and 8-aminoquinoline; the former failure is difficult to understand; but with 8-aminoquinoline the reduction of the diazonium compound is evidently prevented by the formation of the cyclic compound (I) (cf. G.P. 576,119; Cook *et al.*, *J.*, 1943, 404).

(I)

Many other attempts to prepare 8 : 8′-azoquinoline were without success, including reduction of 8-nitroquinoline, oxidation of 8-aminoquinoline, condensation of 8-nitroquinoline with 8-aminoquinoline (cf. Martynoff, *Bull. Soc. chim. France*, 1951, 214; Faessinger and Brown, *J. Amer. Chem. Soc.*, 1951, **73**, 4606), a double Skraup synthesis with 2 : 2′-diaminoazobenzene, and Bucherer-type reaction with 8-hydroxyquinoline, hydrazine hydrate, and hydrazine sulphite (cf. Franzen, *Ber.*, 1905, **38**, 266). Many similar attempts to prepare 3 : 3′-azoquinoline were also fruitless and these two azoquinolines are still unknown.

2 : 2′-Azoquinoline was obtained by Marckwald and Meyer (*Ber.*, 1900, **33**, 1885) by oxidation of the hydrazo-compound formed as a by-product in the preparation of 2-quinolylhydrazine from 2-chloroquinoline and hydrazine hydrate. Some improvements have been effected in this method which has also been adapted to the preparation of 4 : 4′-azoquinoline from 4-chloroquinoline.

* Part VI, *J.*, 1954, 2243.

The ultraviolet absorption spectra of the azonaphthalenes show three main regions of absorption, I, IA, and II (Badger and Buttery, *J.*, 1953, 2156). The spectra of the azoquinolines can also be divided into similar regions (see Table). Region I contains a peak

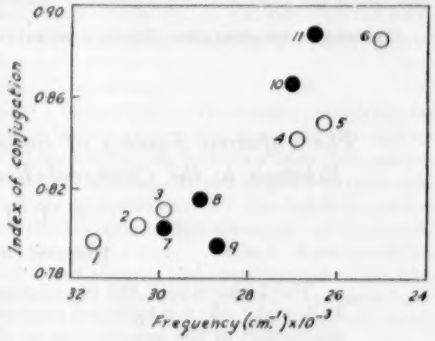
Absorption maxima (Å) *and* log ε (*in parentheses*) *for the azoquinolines in ethanol.*

			Region II	
Azoquinoline	Region I	Region IA	*K*-Band	*R*-Band
2 : 2′-	2200 (4·43)	2600 (4·43)	3480 (4·45)	4640 (2·78)
		—		
		—		
4 : 4′-	2240 (4·52)	2640 (4·21)	3700 (3·92)	—
		—		
		—		
5 : 5′-	2300 (4·69)	—	3780 (4·27)	4700 (3·01)
		—		
		2920 (3·63)		
6 : 6′-	2200 (4·45)	2680 (4·47)	3340 (4·51)	4460 (3·07)
		2840 (4·43)		
		2960 (4·30)		
7 : 7′-	2220 (4·29)	2640 (4·36)	3440 (4·54)	4520 (2·96)
		—		
		2900 (4·22)		

of high intensity at about 2200 Å, similar to that found in the spectra of the azonaphthalenes in this region. Region IA is also similar to that for the azonaphthalenes in that it contains 1—3 peaks at about 2650, 2750, and 2900 Å. Region II contains the *K*- and *R*-bands

Relation between the frequency of the K*-absorption band and the sum of the self-polarisabilities of the positions to which the* N : N *group is attached.*

1, Azobenzene.
2, 2-Phenylazonaphthalene.
3, 2 : 2′-Azonaphthalene.
4, 1-Phenylazonaphthalene.
5, 1 : 2′-Azonaphthalene.
6, 1 : 1′-Azonaphthalene.
7, 6 : 6′-Azoquinoline.
8, 7 : 7′-Azoquinoline.
9, 2 : 2′-Azoquinoline.
10, 4 : 4′-Azoquinoline.
11, 5 : 5′-Azoquinoline.



characteristic of aromatic azo-compounds, the *R*-band being more prominent than with the azonaphthalenes.

With the azonaphthalenes and phenylazonaphthalenes, Badger and Buttery (*loc. cit.*) found a remarkable correlation between the observed frequency of the *K*-band and the conjugating abilities of the position to which the azo-group is attached. The "index of conjugation" was estimated by summing the self-polarisabilities (calculated by the method of molecular orbitals) of the two positions. This comparison has now been extended to the azoquinolines, using the self-polarisabilities for the different positions in the quinoline ring system as calculated by Sandorfy and Yvan (*Bull. Soc. chim. France*, 1950, 131). All the results to date are summarised in the Figure, in which the phenylazonaphthalenes and azonaphthalenes are shown with open circles, and the azoquinolines by black points. The correlation is seen to be less good with the heterocyclic compounds.

Experimental

6 : 6′-*Azoquinoline*.—A solution of 6-aminoquinoline (5 g.) in concentrated sulphuric acid (15 c.c.) and water (100 c.c.) was diazotised at 0° with sodium nitrite (2·5 g.) in water (20 c.c.). Then sodium acetate (50 g.) in water (200 c.c.) was added with stirring, followed by sodium sulphite (5 g.) in water (40 c.c.). The mixture was heated on a water-bath, and then filtered. 6 : 6′-Azoquinoline (4·0 g.) formed, after recrystallisation from xylene, orange needles, m. p.

248—248·5° (Found: C, 76·0; H, 4·4; N, 19·4. Calc. for $C_{18}H_{12}N_4$: C, 76·1; H, 4·3; N, 19·7%). Knueppel (*Annalen*, 1900, **310**, 75) gives m. p. 248°.

5 : 5′-*Azoquinoline*.—5-Aminoquinoline (5 g.), treated as above, yielded 5 : 5′-*azoquinoline* (2 g.), red needles, m. p. 256·5—257° (Found: C, 75·8; H, 4·3; N, 19·6%).

7 : 7′-*Azoquinoline* (2 g. from 3 g. of 7-aminoquinoline) formed orange needles, m. p. 245·5—246° (Found: C, 76·3; H, 4·3; N, 19·4%).

2 : 2′-*Azoquinoline*.—The following method proved superior to that described by Marckwald and Meyer (*Ber.*, 1900, **33**, 1885). 2-Chloroquinoline (19 g.) and 100% hydrazine hydrate (5·7 g.) was heated under reflux at 140° for 4 hr. The resulting solid was washed with water and then taken up in 50% acetic acid (500 c.c.). Oxides of nitrogen, obtained by the action of nitric acid (*d* 1·40) on copper, were passed through the solution until it became deep red. After the addition of aqueous ammonia the product was collected (10 g.; m. p. 228—229°). Recrystallisation from benzene gave 2 : 2′-azoquinoline as orange needles, m. p. 232—233°. Marckwald and Meyer give m. p. 230—231°.

4 : 4′-*Azoquinoline*.—4-Chloroquinoline (2 g.) and 100% hydrazine hydrate (0·6 g.) were heated at 140° in a sealed tube for 2 hr. After cooling, the product was dissolved in 50% acetic acid (50 c.c.) and oxides of nitrogen were then passed through the solution until it became deep red. The solution was cooled, and the red solid collected and dried. The resulting 4 : 4′-*azoquinoline* (0·7 g.; m. p. 200—202°), crystallised from benzene–light petroleum (b. p. 40—100°), formed orange needles, m. p. 201·5—202° (Found: C, 76·4; H, 4·3; N, 19·7%).

Absorption Spectra.—These were determined in absolute ethanol with a Hilger Uvispek spectrophotometer.

Analyses are microanalyses by the C.S.I.R.O. Microanalytical Laboratory, Melbourne. We also thank the C.S.I.R.O. for a research fellowship awarded to one of us (R. G. B.).

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The Infrared Spectra of Substituted Aromatic Compounds in Relation to the Chemical Reactivities of Their Substituents.

By L. J. BELLAMY.

[Reprint Order No. 6077.]

The frequency of the out-of-plane CH deformation absorption of most 1 : 3- and 1 : 3 : 5-substituted aromatic compounds is a linear function of the reactivities of the substituents as determined by Hammett's σ values but halogens are exceptional in behaving as though they had zero σ values. 1 : 4-Substituted aromatic compounds follow a similar relation in those cases in which at least one substituent contains a double bond in conjugation with the ring. The reasons for this are discussed.

CHANGES in the polar environment of a particular grouping within a molecule are reflected in changes in the infrared absorption bands originating in that group. In many cases this is best shown by studies of intensity and a number of important advances have recently thus been made (Mecke, *J. Chem. Phys.*, 1952, **20**, 1935; Barrow, *ibid.*, 1953, **21**, 2008; Jones, Ramsey, Keir, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 80; Thompson, Institute of Petroleum Conference on Molecular Spectroscopy, London, 1954). However, in some cases changes in the frequency can also be correlated with the polarity of substituent groups and this then offers a convenient approach, as the measurement of absolute extinction coefficients is attended by considerable instrumental difficulties.

Goulden (*Spectrochim. Acta*, 1954, **6**, 129) has shown that there is a linear relation between the OH stretching frequencies of monomeric aliphatic acids and their pK_a values, whilst similar but different relations hold for aromatic acids and for phenols. Flett (*Trans. Faraday Soc.*, 1948, **44**, 767) has pointed out that the characteristic frequencies of acid, aldehyde, and amino-groups in aromatic compounds can be correlated with Hammett's

σ functions (Hammett, " Physical-Organic Chemistry," McGraw Hill, New York, 1940, p. 188), and similar relations have been reported by Ingraham, Corse, Bailey, and Stitt (*J. Amer. Chem. Soc.*, 1952, **74**, 2297) for substituted phenols and catechols, and by Fuson, Josien, and Shelton (*ibid.*, 1954, **76**, 2526) for an extensive series of substituted aromatic carbonyl compounds.

Basically, Hammett's σ values measure changes in the electron density of a carbonyl group attached to an aromatic ring. They can therefore be regarded as being a measure of the overall effect of the substituted ring rather than of the localised effect of the substituent. This is supported by the additivity of the effects of two or more substituents which appear to be without effect upon each other. The use of different values for the same group in the *meta*- and *para*-positions arises from the conjugation of the latter with the carbonyl group which results in a difference in the overall effects of the substituted rings.

It was thought therefore of interest to see whether a relation could be found between σ values and some general vibrational mode of the ring itself. For this purpose we studied the out-of-plane CH deformations of 1 : 3-, 1 : 4-, and 1 : 3 : 5-substituted aromatic compounds, as we had previously noted regularities in this series. These deformation modes give rise to what are normally the strongest bands in the low-frequency region of the spectrum, and are therefore usually easy to identify. They occur in the regions of 775, 810, and 850 cm.$^{-1}$ and can be regarded as being derived respectively from motions involving three adjacent ring-hydrogen atoms, two adjacent ring-hydrogen atoms, and of an isolated ring-hydrogen atom situated between two substituents (Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397). 1 : 3-Disubstituted compounds therefore show the first and the last of these absorptions. Aromatic compounds with two or more adjacent substituents have not been considered as steric effects often cause the substituents to lie out of the plane of the ring. In consequence, σ values derived from kinetic studies do not in these cases provide a true measure of the polar effects of the substituents.

Experimental.—The spectra were obtained with a Perkin-Elmer 21 recording spectrometer with a rock-salt prism. Samples were determined as solids dispersed in liquid paraffin and/or in solution in suitable solvents. For the particular frequencies studied very little difference is found between the solid and the solution spectra. The observed CH out-of-plane deformation absorptions are listed in Tables 1 and 3 (below) and are discussed below. The bands have been identified as being the strongest in the appropriate spectral regions after allowance for any bands due to particular substituents known to absorb in the same region. A few 1 : 3-disubstituted materials show a number of strong bands in the expected regions, and identification of the two δCH absorptions was then based on the expectation that any polar effects would affect them both to approximately the same extent so that they would retain their usual spacing of about 75 cm.$^{-1}$ apart.

Results and Discussion

(a) 1 : 3- *and* 1 : 3 : 5-*Substituted Compounds.*—The observed frequencies of the out-of-plane CH deformations of the compounds studied are listed in Table 1, together with some of Cole and Thompson's values (*Trans. Faraday Soc.*, 1950, **46**, 103). They are plotted in

TABLE 1. *Out-of-plane ring* CH *deformation frequencies* (*cm.*$^{-1}$).

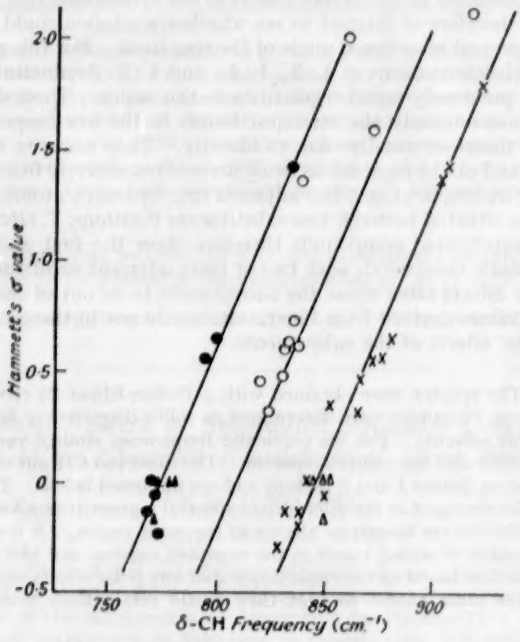
1 : 3-Substituted compounds						1 : 3 : 5-Substituted compounds			
Me_2	769	838	* $(Cl)_2$	780	—	Me_3	838	$(OEt)_3$	866
Me, NO_2	801	880	* Cl, I	773	—	Me_3, NO_2	872	Me_3, NH_2	828
$(NO_2)_2$	835	906	* Br, Me	773	—	Me, $(NO_2)_2$	903	CO_2H, $(NO_2)_2$	921
OH, Me	772	850	* F, CH_3	778	—	$(NO_2)_3$	917	* $(Cl)_3$	853
$(OH)_2$	772	842	NH_2, Cl	771	849	Me_3, OH	832	* $(Br)_3$	850
NH_2, NO_2	795	866				OH, $(OEt)_2$	865	† $(F)_3$	854
						$(OMe)_3$	852		

* Cole and Thompson (*loc. cit.*). † Nielsen, Liang, and Smith, *Discuss. Faraday Soc.*, 1950, **9**, 177.

the Figure directly against the sum of Hammett's *meta*-σ values for the substituents. It will be seen that, with the exception of the halogen derivatives (which have not been plotted

on this basis), the points lie reasonably close to one or other of two parallel straight lines. The first of these connects points involving the vibration of 3 adjacent hydrogen atoms, and the second connects points involving the vibration of a lone hydrogen atom with substituents on either side. It will be seen also that a similar line derived from those 1 : 4-substituted materials in which such a plot is considered to be appropriate (see below) appears to be roughly parallel with the other two, and midway between them.

When plotted on the same basis, the halogen derivatives show a wide scatter but it is significant that they all fall very close to these lines if the halogens are assumed to have zero σ values (see Fig.). The numbers involved are thought to be too great for this to be coincidental but no satisfactory explanation can be offered yet.



δ-CH vibrations of: ● 3 adjacent ring hydrogen atoms.
▲ ,, ,, ,, (halogen-substituted).
○ 2 ,, ,, ,,
× An isolated ring hydrogen atom
△ ,, ,, ,, (halogen-substituted).

Hammett's σ values are not readily available for a number of substituents—particularly the larger alkyl groups—which it would have been interesting to plot in this way. However, an alternative check on the validity of this relation can be obtained by deriving σ values from the observed frequencies of a few simple alkylbenzenes and employing these in the prediction of the frequencies of other compounds. Thus the 1 : 3 : 5-derivatives of triethyl-, tri*iso*propyl-, and tri-*tert.*-butyl-benzene absorb respectively at 865, 870, and 874 cm.$^{-1}$, corresponding to σ values of +0·14, +0·18, and +0·21 for the ethyl, *iso*propyl, and *tert.*-butyl group (McCaulay, Lien, and Launer, *J. Amer. Chem. Soc.*, 1954, **76**, 2554). The use of these values in the prediction of the CH deformation frequencies of other alkylbenzenes gives the results shown in Table 2, in which they are compared with observed values. The agreement for the principal bands is good, despite the fact that the positive σ values imply that relative to the methyl group, there is an electron withdrawal from the ring

rather than an electron donation which would be expected from the theory of hyperconjugation. The agreement in respect of the second CH deformation absorption of 1 : 3-substituted compounds near 840 cm.$^{-1}$ does not appear to be good, but this band is relatively weak in hydrocarbons and it is correspondingly less easy to identify.

TABLE 2. *Out-of-plane ring* CH *deformation frequencies of alkylbenzenes.*

Substituents	ν, calc. (cm.$^{-1}$)	ν, found (cm.$^{-1}$)	Substituents	ν, calc. (cm.$^{-1}$)	ν, found (cm.$^{-1}$)
1 : 3 : 5-Me_3, Et *	842	845	1 : 3-Me, Et † ...	778	781
Me_2, Pr^i *	848	846	Et_3 †	787	792
Me_2, Bu^t *	850	847	Pr^i_3 †	793	793
Me, Et_2 *	856	855	Me, Bu^t ‡	781	781
Me, Pr^i_2 *	858	858	Et, Bu^t ‡	791	794
Me, Bu^t_2 *	862	859			

* McCaulay *et al.* (*loc. cit.*). † A.P.I. Spectra. ‡ Schlatter and Clark, *J. Amer. Chem. Soc.*, 1953, **75**, 361.

1 : 4-*Substituted Compounds.*—Hammett's σ values for *para*-substituents differ from the corresponding *meta*-values, as additional mesomeric effects are called into play by the direct conjugation of the substituents, through the ring, with the carboxyl group. These *para*-σ values will therefore be appropriate only to those compounds which contain a similar conjugated substituent. In other cases the polar effects of the substituents will often be in direct opposition to one another and the overall effects upon the δCH ring vibrations will be relatively small.

It is therefore to be expected that any relation which may exist between Hammett's *para*-σ values and δCH ring frequencies will be confined to compounds containing an unsaturated group in conjugation with the ring. In other compounds these frequencies will tend to group themselves about the points corresponding to a zero σ value. This appears to be essentially what is found. The results are given in Table 2 and it will be seen from these and from the Figure that the compounds studied which contain a conjugated group follow a roughly linear relation with Hammett's σ values, whilst the remainder group themselves about 810 cm.$^{-1}$. In plotting the Figure, Hammett's *para*-σ values have been used throughout with the exception of that for the *p*-dimethylamino-group. This has been found to be unsatisfactory in previous cases (Flett, *loc. cit.*) and is based on limited data. Instead, we have used a value calculated directly from the pK_a value of *p*-dimethylaminobenzoic acid.

TABLE 3. *Out-of-plane ring* CH *deformation frequencies of* 1 : 4-*substituted compounds* (*cm.*$^{-1}$).

Substituents	ν	Substituents	ν	Substituents	ν	Substituents	ν
Cl_2	818	Me, NH_2	814	NMe_2, CHO	824	Me, NO_2	834
$(OH)_2$	826	Me, NMe_2	806	Cl, CHO	839	$(NO_2)_2$	872
$(NH_2)_2$	826	Me, OH	815	NO_2, NH_2	838	NO_2, NMe_2	820
Cl, NH_2	819	* F, Me	817	NO_2, CHO	850	* Br, I	807
Cl, OH	822	* Cl, Me	809	OH, CHO	836	* Cl, I	811
Br_2	806	* Br, Me	803	OH, COMe	830	* F_2	805
Me_2	798	* Br, Cl	816	OMe, COMe	833	* Me, I	800

* Cole and Thompson (*loc. cit.*).

Thanks are offered to the Chief Scientist, Ministry of Supply, for permission to publish this paper.

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The Mechanisms of Retardation and Inhibition in Radical Polymerizations. Part II. The Effects of p-Benzoquinone upon the Sensitized Polymerization of Styrene.*

By J. C. Bevington, N. A. Ghanem, and H. W. Melville.

[Reprint Order No. 6181.]

The effects of *p*-benzoquinone upon the sensitized polymerization of styrene at 60° have been studied in detail by using [^{14}C]benzoquinone and azo[^{14}C]*iso*butyronitrile as sensitizer. There is initially a slow polymerization, during which all the *p*-benzoquinone is consumed and polymer of low molecular weight is produced; the slow reaction changes fairly abruptly to a fast reaction which has all the characteristics of the normal polymerization. During the slow reaction most of the quinone becomes incorporated in the polymer although a small amount of it reacts directly with the radicals produced from the sensitizer.

In this paper a study of the effects of *p*-benzoquinone upon the bulk polymerization of styrene initiated by azo*iso*butyronitrile is reported. The work involved the use of [^{14}C]*p*-benzoquinone and azo[^{14}C]*iso*butyronitrile; these substances had already been used in a study of the effect of the quinone upon the polymerization of methyl methacrylate (Bevington, Ghanem, and Melville, *Trans. Faraday Soc.*, **1955**, in the press).

The main uses of methods involving labelled reagents in a study of this sort can be summarized as follows: (i) It is possible to see if a particular substance becomes chemically incorporated in polymer; then if the number-average molecular weight of the polymer is known, the exact amount of the substance combined in each polymer molecule can be calculated.

(ii) By means of isotope dilution analysis, it is possible to decide what substances of low molecular weight are formed during the polymerization, and also to determine their exact yields.

(iii) If an abnormality is introduced into the regular structure of a polymer, *e.g.*, if a molecule of *p*-benzoquinone is incorporated in a polystyrene chain, it may be possible to find the way in which it is linked. Suppose that the abnormal unit in the structure is radioactive and that the polymer is then treated with chemical reagents which cleave specific linkages. If a particular reagent causes the activity to be lost from the polymer, it is likely that the abnormality is bound into the polymer by a certain type of chemical linkage.

(iv) The rates of initiation in radical polymerizations can be found by a straightforward method using labelled initiator (Bevington, Bradbury, and Burnett, *J. Polymer Sci.*, **1954**, **12**, 469); reaction involving an added substance may be revealed by study of rates of initiation.

Information obtained in these ways can lead to a full understanding of the mechanisms by which additives affect polymerizations. In theory it would be possible to obtain this information by conventional analytical methods, but in practice the small weights of the substances involved and the complexities of the mixtures combine to make isotopic methods essential.

The effects of *p*-benzoquinone upon the sensitized polymerizations of styrene and methyl methacrylate appear to be very different. It is shown in this paper, however, that the differences are not fundamental, and an attempt is made to account for them in terms of the relative reactivities of styrene and methyl methacrylate and of the corresponding radicals.

Experimental

Materials.—Descriptions have been given for the procedures used in the purification of monomer and solvents, and in the preparation of azo[^{14}C]*iso*butyronitrile, tetramethylsuccinonitrile, and [^{14}C]*p*-benzoquinone (Bevington, Melville, and Taylor, *J. Polymer Sci.*, **1954**, **12**,

* Part I, Bevington, Ghanem, and Melville, *Trans. Faraday Soc.*, in the press.

449; Bevington, *J.*, 1954, 3707; Bevington, Ghanem, and Melville, *loc. cit.*). The diether $C_6H_4(O{\cdot}CMe_2{\cdot}CN)_2$ was prepared by the method described by Bickel and Waters (*J.*, 1950, 1764). The diacetate of quinol was prepared from quinol and acetic anhydride and recrystallized from ethanol. Quinol was recrystallized from water.

Methods.—Reaction tubes were charged with initiator, *p*-benzoquinone, and monomer and degassed as described previously. The polymerizations were followed dilatometrically; it was supposed that, at 60°, 17·58% contraction is equivalent to 100% polymerization. Polymers were isolated and reprecipitated as described for polymers of methyl methacrylate (Bevington, Ghanem, and Melville, *loc. cit.*). When isotope dilution analyses were performed, the carrier and the reaction mixture were mixed in benzene solution before precipitation of the polymer. After the polymer had been filtered off, the filtrate was evaporated to dryness under a vacuum at low temperature; the solid residue was then purified by repeated crystallization.

The number-average molecular weights of polymers were determined by osmometry. The specific activities of radioactive materials were compared by the method of gas-counting; the materials were oxidised to carbon dioxide by wet oxidation. These assay procedures have been described fully (Bevington, Melville, and Taylor, *loc. cit.*). In the experimental results, the counting rates are directly proportional to the ^{14}C : ^{12}C ratios in the samples being measured.

Certain samples of polystyrene were treated with trifluoroacetic anhydride and acetic acid. The polymer (about 300 mg.), trifluoroacetic anhydride (3 g.), glacial acetic acid (0·8 g.), and dry toluene (10 c.c.) were gently refluxed for 9 hr. The polymer was precipitated in the usual way in a large volume of cold methanol; the recovered polymer was dissolved in benzene and precipitated again in methanol.

Results.—Separation tests. It is essential that polymers prepared in the presence of labelled quinone or labelled initiator should be separated completely from uncombined active materials of low molecular weight. It has been shown that the technique of double precipitation removes almost every trace of uncombined initiator from polystyrene (Bevington, Melville, and Taylor, *loc. cit.*) and of uncombined *p*-benzoquinone from poly(methyl methacrylate) (Bevington, Ghanem, and Melville, *loc. cit.*). Tests on the separation of polystyrene from *p*-benzoquinone are now reported. In the first test, polystyrene was precipitated from benzene solution by using methanol containing dissolved [^{14}C]*p*-benzoquinone, and then the polymer was filtered off, washed, dried, and assayed; the polymer was redissolved in benzene, precipitated in pure methanol, washed, dried, and assayed. In the second test the inactive polymer and active quinone were mixed in benzene solution before precipitation in methanol. In both tests the ratio of the weight of quinone to the weight of polymer was greater than in any of the polymerization experiments. The tests are summarized in Table 1. The separation of polymer and quinone is clearly quite satisfactory.

TABLE 1.

	Test 1	Test 2
Calc. Counts/min. : for no separation of polymer and quinone	1633	4660
Obs. after 1 pptn.	1·5	2
Obs. after 2 pptns.	0	2

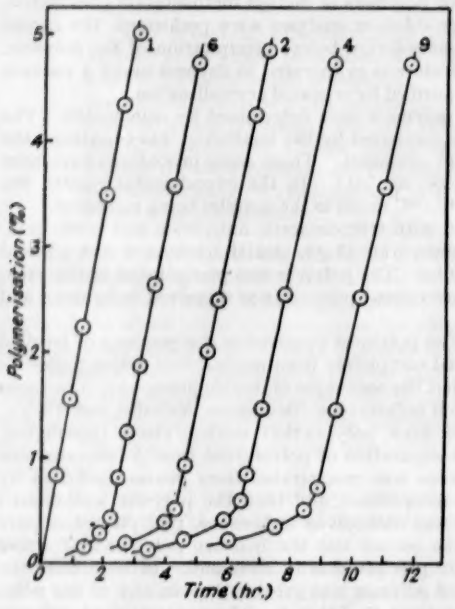
Polymerizations with labelled initiator. The presence of *p*-benzoquinone caused the polymerization of styrene initiated by azo*iso*butyronitrile to be very slow in its early stages. The rate increased slightly with time but at one point there was quite a marked increase in rate to a value which was maintained at least as far as 5% conversion. Typical conversion–time plots are shown in the Figure. Evidently the quinone was not a complete inhibitor of the polymerization. Induction periods are recorded as the intercepts on the time axis of the linear parts of the conversion–time plots. The colour of the *p*-benzoquinone gradually disappeared during the induction period. The length of the induction period increased and the final steady rate decreased slightly as the initial concentration of quinone was raised.

Experiments with a fixed concentration of ^{14}C-initiator and various concentrations of unlabelled quinone are summarized in Table 2. These polymerizations were allowed to proceed to 5% conversion. The end-groups refer to $CMe_2{\cdot}CN$ fragments from the initiator incorporated in the polymer.

A mixture of polymers 2, 3, and 4, having a counting rate of about 350 counts/min., was dissolved in chloroform and precipitated in diethyl ether which is a solvent for polystyrene of low molecular weight (Staudinger and Heuer, *Z. phys. Chem.*, 1934, *A*, 171, 129). The precipitated polymer was redissolved in benzene and precipitated in methanol; 78% of the original polymer

was recovered. After drying, the recovered polymer had a counting rate of 213 counts/min.; if this polymer contains two initiator fragments per molecule, this activity corresponds to a molecular weight of 244,000.

Polymerizations with labelled benzoquinone. Experiments involving unlabelled initiator and [^{14}C]*p*-benzoquinone are summarized in Table 3. Expts. 6, 7, 8, and 9 were carried to 5% conversion. In expt. 10 the reaction was stopped after 1·93% conversion (calculated from



Conversion–time plots for typical experiments involving styrene, azoisobutyronitrile, and p-benzoquinone. (The numbering corresponds to that in Tables 2 and 3.)

the contraction); 0·25 g. of polymer was recovered whereas by calculation 0·30 g. should have been formed. In expt. 11, the calculated conversion was 0·86% but only about 77% of the calculated weight of polymer was recovered after precipitation in methanol, and its molecular weight was too low for osmometry. Assay of polymer no. 11 gave 700 counts/min. after 1

TABLE 2.

Expt. no.	Initiator concn. (g./l.)	Quinone concn. (g./l.)	Induction period (min.)	Steady rate (%/hr.)	*M*	counts/min. for polymer *	No. of end-groups per polymer mole
1	0·500	0	0	1·750	215,000	242	2·00
2	0·503	0·075	240	1·563	—	351	—
3	0·485	0·080	240	1·564	143,000	389	2·14
4	0·505	0·123	365	1·480	145,500	332	1·86
5	0·517	0·129	400	1·483	—	—	—

* counts/min. for initiator = 500,000.

TABLE 3.

Expt. no.	Initiator concn. (g./l.)	Quinone concn. (g./l.)	Induction period (min.)	Steady rate (%/hr.)	*M*	counts/min. polymer *	No. of quinone moles per polymer mole
6	0·500	0·050	120	1·698	143,000	29	0·53
7	0·503	0·055	150	1·624	150,000	28	0·54
8	0·514	0·101	380	1·566	142,500	49	0·90
9	0·493	0·157	505	1·460	153,500	86	1·70
10	0·486	0·119	—	—	63,000	227	1·85
11	0·503	0·121	—	—	—	561	—

* counts/min. for *p*-benzoquinone = 99,400.

precipitation and 561 counts/min. after 2 precipitations. The comparatively high rate shows that the polymer was quite rich in *p*-benzoquinone but the difference between the two values confirms that the molecular weight was low, since some of the smaller molecules were lost during the second precipitation. In Table 3 the numbers of *p*-benzoquinone molecules combined in each polymer are recorded.

A sample of polystyrene of average molecular weight near 150,000 and containing [^{14}C]-*p*-benzoquinone was precipitated in diethyl ether to remove material of comparatively low molecular weight, as described in a previous section. The counting rate was reduced from 35 to 6 counts/min., showing that the combined quinone was present in those polymer molecules which were of small size, and that in those molecules which were insoluble in ether there was little or no combined *p*-benzoquinone.

Experiments involving analyses. In order to see if the *p*-benzoquinone was completely consumed during the induction period, a reaction mixture containing [^{14}C]benzoquinone was made up and the quantity remaining at the end of the induction period was found by isotope dilution analysis. The original weight of the [^{14}C]quinone was 1·94 mg. and the weight of unlabelled quinone added as carrier was 415·6 mg.; the counting rate of the quinone after purification was 4 counts/min. The weight of [^{14}C]*p*-benzoquinone remaining in the mixture was therefore 0·017 mg., showing that less than 1% of the original material remained at the end of the induction period.

There may be direct reaction between *p*-benzoquinone and radicals formed by dissociation of the initiator, in which case the diether $C_6H_4(O{\cdot}CMe_2{\cdot}CN)_2$ (I) should be found in the reaction mixture (Bickel and Waters, *loc. cit.*). The quantity of this material can be determined by isotope dilution analysis starting with either labelled quinone or labelled azo*iso*butyronitrile. In expt. 11, 3·3 mg. of [^{14}C]*p*-benzoquinone were used originally and 436·6 mg. of inactive diether (I) were added as carrier; the counting rate for the purified diether was 12 counts/min. The weight of (I) in the reaction mixture was therefore 0·123 mg., equivalent to 0·054 mg. of *p*-benzoquinone. Expt. 11 was interrupted at the end of the induction period so that all the quinone was consumed; thus 1·7% of the original quinone was converted into the diether. A similar analysis was performed in expt. 3 which involved ^{14}C-initiator and was allowed to proceed to 5% conversion. The weight of carrier was 280·3 mg. and the counting rate of the purified material was 58 counts/min.; the weight of (I) in the reaction mixture was therefore 0·057 mg., which corresponds to 2% of the *p*-benzoquinone present originally.

In expt. 12, a solution of azo[^{14}C]*iso*butyronitrile (13·62 mg.) and *p*-benzoquinone (4·37 mg.) in styrene (27·4 c.c.) was kept at 60° for 8½ hr. Isotope dilution analysis for tetramethylsuccinonitrile was performed; the weight of carrier was 555·3 mg. and the counting rate of the purified material was 480 counts/min. The weight of the dinitrile in the reaction mixture was therefore 0·534 mg.

Experiments involving trifluoroacetic anhydride. Polymer no. 9 (326·8 mg.) containing [^{14}C]*p*-benzoquinone was treated with trifluoroacetic anhydride and acetic acid as described in a previous section. After precipitation twice in methanol and drying, the counting rate of the polymer was 27 counts/min.; the counting rate for the original polymer was 86 counts/min. The combined filtrates from the precipitations were concentrated under reduced pressure and divided into two equal portions. To one portion pure quinol diacetate (349·6 mg.) was added; the solvent was removed under reduced pressure and the diacetate was purified by recrystallization; its counting rate was 11·5 counts/min. To the other portion, 2N-sodium hydroxide (80 c.c.) and pure quinol (634·8 mg.) were added; after refluxing for 30 min. the liquid was neutralized with hydrochloric acid. The liquid was distilled off under reduced pressure and from the residual solid a sample of pure quinol was prepared by repeated crystallization; its counting rate was 11 counts/min.

A sample of polystyrene with labelled $CMe_2{\cdot}CN$ end-groups, but completely free from *p*-benzoquinone, was treated with the trifluoroacetic anhydride reagent under the same conditions as in the experiment described above. The counting rate for the polymer was reduced from 234 to 209 counts/min.; the treatment did not cause the weight of polymer to increase.

Discussion

General Features of the System.—In this paper *p*-benzoquinone is referred to as an inhibitor of the sensitized polymerization of styrene. The conversion–time plots in the Figure show, however, that polymerization is not completely inhibited in the so-called induction period. The transition from a slow reaction to a fast one is fairly abrupt and

the character of the polymer produced during the slow reaction is very different from that of the polymer produced in the later stages, and the use of the term inhibitor is therefore justified; it must be recognised, however, that, compared with a material such as diphenylpicrylhydrazyl, the quinone is inefficient as an inhibitor.

It was shown by isotope dilution analysis that less than 1% of the *p*-benzoquinone remained at the end of the induction period. It is believed that during the fast reaction the rate is that which would be expected if the quinone were absent; further, the molecular weight of the polymer produced after the induction period is the same as that of polymer formed in the complete absence of *p*-benzoquinone. The evidence for these views is now presented.

The steady rates observed after the induction periods are all slightly less than that in a normal polymerization (see Tables 2 and 3); the differences can be accounted for by consumption of initiator during the induction periods. The velocity constant for the decomposition of azo*iso*butyronitrile is known, and therefore the quantity of initiator remaining at the end of the induction period can be calculated. The observed rates can then be corrected to an initiator concentration of 0·500 g./l. by using the relation

$$\text{rate} \propto (\text{initiator concentration})^{\frac{1}{2}}$$

The velocity constant for the decomposition of the initiator is taken as $1{\cdot}20 \times 10^{-5}$ sec.$^{-1}$ at 60° (Bevington, *Trans. Faraday Soc.*, in the press). The corrected rates of polymerization are shown in Table 4.

TABLE 4.

Expt. no.	1	2	3	4	5	6	7	8	9
Initiator (%) remaining after induction period	100	84·2	84·2	77·1	75·3	91·7	90·0	83·0	69·8
Corrected rate (%/hr.)	1·75	1·65	1·69	1·68	1·68	1·77	1·70	1·70	1·76

There is little difference between the corrected rates, showing that in the main the differences between the rates observed in the various experiments were due to changes in initiator concentration. There is a tendency for the corrected rates in expts. 2—9 to be a little below that for expt. 1. This is to be expected, since the recorded induction periods are a little less than the times required for the steady rates of polymerization to be attained, and therefore the correcting factors are not quite large enough. It is clear also that during the induction period the quinone is not converted into substances which subsequently act as retarders.

Several observations show that the polymer produced during the induction period is of low molecular weight. Normally, the polymerizations were allowed to proceed to 5% conversion but in expts. 10 and 11 the reactions were stopped near the end of the induction period; in these cases the polymers were of low molecular weight and there was appreciable loss of polymer during precipitation. The experiments involving precipitation of polymers in diethyl ether, which is a solvent for polystyrene of molecular weight less than about 25,000, show that the polymers formed after the induction period contain no quinone and have a molecular weight by end-group analysis close to that of a polymer formed in a normal polymerization (the molecular weights are 244,000 and 215,000). In these experiments about 22% of the polymer remained in the ether solution. The unrecovered polymer is probably that formed during the induction period containing *p*-benzoquinone and having low molecular weight, but it is likely also to contain some of the polymer formed during the fast reaction; this would be the material at the low-molecular-weight end of the distribution. It is possible therefore to explain why the molecular weight of the material remaining after ether-extraction is a little greater than that of the normal polymer.

Ordinarily in polymers of styrene prepared at 60° by use of azo*iso*butyronitrile as initiator, there are two initiator fragments combined in each polymer molecule (Bevington, Melville, and Taylor, *J. Polymer Sci.*, 1954, **14**, 463). This shows that when polystyrene radicals interact they do so by combination. In both polymers 3 and 4, the number of initiator fragments per polymer is close to 2, even although these polymers contain appreciable numbers of molecules formed at early stages in the reactions. It is clear that almost all polymer radicals are destroyed by combination at all stages in the reaction.

It is important to consider whether *p*-benzoquinone interferes in the initiation of polymerization. The relative numbers of molecules of quinone and initiator consumed during the induction periods are given in Table 5. The last line of the Table gives the relative quantities of *available* radicals produced from the initiator during the induction periods; it must be noted that 1 mole of initiator gives 2 moles of radicals, and that, of the radicals

TABLE 5.

Expt. no.	2	3	4	5	6	7	8	9
Quinone consumed (moles)	6·94	7·41	11·39	11·95	4·63	5·09	9·35	14·54
Initiator decomposed (moles)	4·83	4·65	7·05	7·80	2·52	3·03	5·32	9·14
Available radicals produced (moles)	6·76	6·51	9·87	10·92	3·53	4·24	7·45	12·80

produced during the decomposition of the initiator, only about 70% are available for reaction with other substances (Bevington, *Nature*, 1955, **175**, 477) as shown by the fact that products of the interaction of initiator radicals are produced (see expt. 12). The rough agreement between the number of available radicals generated and the number of quinone molecules consumed does not indicate a direct reaction between the radicals and these molecules, since only small quantities of the products arising from such a reaction are found. Bickel and Waters (*loc. cit.*) showed that when 2-cyano-2-propyl radicals are generated in toluene solution in the presence of *p*-benzoquinone, the ethers (I) and $C_6H_4(OH)(O{\cdot}CMe_2{\cdot}CN)$ (II) are formed; the yield of the former is about 4 times that of the latter, based on the quinone. Analyses for the ether (I) in expts. 3 and 11 showed that only about 2% of the quinone appeared as this product, and therefore about 90% of the quinone must have been incorporated in polymeric material. This shows clearly that the quinone exerts its effect by reacting with polymer radicals at an early stage in their growth rather than with the radicals formed directly by dissociation of the initiator. Cohen (*J. Polymer Sci.*, 1947, **2**, 511) also presented evidence leading to this conclusion.

It is possible to compare the velocity constants for the alternative reactions

$$\cdot CMe_2{\cdot}CN + O{:}C_6H_4{:}O \longrightarrow CMe_2(CN){\cdot}O{\cdot}C_6H_4{\cdot}O{\cdot}$$
$$\cdot CMe_2{\cdot}CN + CH_2{:}CHPh \longrightarrow CMe_2(CN){\cdot}CH_2{\cdot}CHPh{\cdot}$$

Consider experiment 3. Analysis for the ether (I) showed that 2% of the quinone appeared as this product; it is probable therefore that about 8% was converted into (II). The relative figures in Table 5 being used, these quantities of quinone are equivalent to 0·15 mole and 0·30 mole of azo-compound respectively. About 10% of the initiator decomposing during the induction period appeared therefore as products not containing styrene; a further 30% of the decomposed initiator reacted with neither quinone nor monomer; the remaining 60% must have reacted with styrene. The concentration of styrene was near 8·5 moles/l. and the average concentration of quinone during the induction period was about 4×10^{-4} mole/l. Putting

$$\frac{\text{Rate of reaction of radicals with quinone}}{\text{Rate of reaction of radicals with monomer}} = \frac{k_x[R][Q]}{k_i[R][M]} = \frac{10}{60}$$

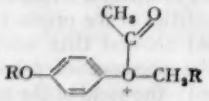
where [R], [Q], and [M] are the concentrations of radicals, quinone, and monomer respectively, we find k_x/k_i to be about 3500.

Structures of Polymers containing p-*Benzoquinone.*—Mechanisms by which *p*-benzoquinone might react with polymer radicals have been summarized by Flory (" Principles of Polymer Chemistry," Cornell Univ. Press, Ithaca, New York, 1953, p. 164). Bickel and Waters (*loc. cit.*) showed that the radical $\cdot CMe_2X$, where X is CN or CO_2CH_3, attacks *p*-benzoquinone at the oxygen atom giving $CXMe_2{\cdot}O{\cdot}C_6H_4{\cdot}O{\cdot}$ as the first product; they found no evidence for the occurrence of nuclear substitution in the quinone. The radicals studied by Bickel and Waters have reactivities similar to those present in polymerizing styrene or methyl methacrylate, and it is likely therefore that polystyrene containing combined *p*-benzoquinone can be represented as $RO{\cdot}C_6H_4{\cdot}OR$.

The results of the preliminary experiments involving trifluoroacetic anhydride are also consistent with the belief that the quinone is bound into the polymer by two ether linkages. There is evidence that the trifluoroacetic anhydride reagent causes the cleavage of ether

linkages (Bourne, Burdon, and Tatlow, personal communication). A polymer containing [^{14}C]*p*-benzoquinone and having the formula shown above should lose its activity if treated with the reagent, and in fact the specific activity of polystyrene no. 9 was reduced to less than one-third of its original value. A complicating factor is that the introduction of acetyl groups into certain aromatic substances can be promoted by trifluoroacetic anhydride (Bourne, Randles, Stacey, Tatlow, and Tedder, *J. Amer. Chem. Soc.*, 1954, **76**, 3206). The reduction of the specific activity of polymer no. 9 might therefore be due in part to the addition of non-radioactive carbon atoms to the polymer molecules. If this effect were the sole reason for the reduction in activity, it would imply that 8 acetyl groups become attached to each monomer unit, which is most improbable. Further, the control experiment with polystyrene containing labelled end-groups but no quinone showed that the introduction of acetyl groups is comparatively unimportant.

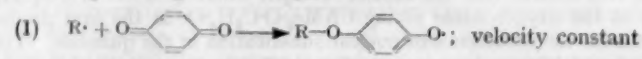
It is believed (Bourne, Randles, *et al.*, *loc. cit.*) that in a mixture of trifluoroacetic anhydride and acetic acid, the mixed anhydride $CF_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$ and the ions $CH_3{\cdot}CO^+$ and $CF_3{\cdot}CO{\cdot}O^-$ are formed. The cation may attack an ether linkage in the polymer to form an oxonium ion thus:



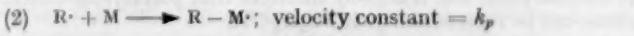
This oxonium ion may break down to give $RO{\cdot}C_6H_4{\cdot}O{\cdot}CO{\cdot}CH_3$ and $R{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}CF_3$ (by reaction of the other fragment with $CF_3{\cdot}CO{\cdot}O^-$) or alternatively it might break down to $RO{\cdot}C_6H_4{\cdot}O{\cdot}CO{\cdot}CF_3$ and $R{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}CH_3$. As a result of the cleavage with trifluoroacetic anhydride and acetic acid, the *p*-benzoquinone which is split out of the polymer may be present in three forms, *viz.*, p-$CH_3{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}O{\cdot}CO{\cdot}CH_3$ (III), p-$CH_3{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}O{\cdot}CO{\cdot}CF_3$ (IV), and p-$CF_3{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}O{\cdot}CO{\cdot}CF_3$ (V). Isotope dilution analysis revealed the presence of 0·134 mg. of diacetate (III), equivalent to 0·075 mg. of *p*-benzoquinone. Quinol would be formed from all three esters on hydrolysis; analysis showed that 0·140 mg. of quinol was produced, equivalent to 0·137 mg. of *p*-benzoquinone. If the reduction in the specific activity of the polymer were due solely to the removal of *p*-benzoquinone, the weight of quinone cleaved out of the polymer must have been 0·268 mg. The discrepancy between the two weights of quinone can be explained by the introduction of acetyl groups into the benzene rings of the polymer. Some of the acetyl groups might be substituted in the benzene rings of the styrene units, and some might be situated in the benzene rings of the esters (III), (IV), and (V). Substitution in the styrene units was discussed above; if acetyl groups had been introduced into the esters, the resulting compounds would not have shown up in the analyses for the quinol and its diacetate.

It is concluded that the experiments involving trifluoroacetic anhydride show that some at least of the *p*-benzoquinone is incorporated in polystyrene by ether linkages. The quinone thus bound can be split out by means of trifluoroacetic anhydride and acetic acid; one of the products is quinol diacetate, but esters of quinol containing fluorine are also formed.

Comparison of Methyl Methacrylate and Styrene.—Comparison of the effects of *p*-benzoquinone upon the sensitized polymerizations of styrene and methyl methacrylate shows that the addition of a molecule of the quinone to the polymer radical occurs more readily for styrene than for methyl methacrylate. The interaction between a polymer radical and a molecule of *p*-benzoquinone is represented as



and the propagation reaction as



Thus

$$\frac{\text{Rate of reaction (1)}}{\text{Rate of reaction (2)}} = \frac{k_r[R][Q]}{k_p[R][M]} = \frac{k_r[Q]}{k_p[M]}$$

where [R], [Q], and [M] are as defined on p. 2827. For the retarded polymerization of methyl methacrylate and the slow polymerization of styrene, [Q] and [M] are about equal. The difference between the two systems can be expressed as

$$(k_r/k_p) \text{ styrene} > (k_r/k_p) \text{ methyl methacrylate}$$

The values of these ratios can be estimated as follows. Consider expt. **3**. During the induction period about 0·8% of the monomer polymerized and all the quinone was consumed; considering 1 l. of reaction mixture, 0·07 mole of styrene and $7·5 \times 10^{-4}$ mole of *p*-benzoquinone were incorporated in polymer. The ratio k_r/k_p can be calculated in the same way as the ratio k_r/k_t, and it is found to be 227; there is therefore a marked difference between these ratios. In an experiment with methyl methacrylate, *viz.*, expt. no. 20 in the paper by Bevington, Ghanem, and Melville (*loc. cit.*), 1 molecule of quinone was combined with 1305 molecules of methyl methacrylate; in this experiment the average concentration of quinone can be taken as $1·5 \times 10^{-3}$ mole/l. (*i.e.*, not very different from its initial value) and the concentration of monomer as 9 moles/l. The value of k_r/k_p for methyl methacrylate is therefore about 4·5. The value at 60° for k_p for methyl methacrylate is about three times that for styrene, and therefore k_r for styrene is 16 times k_r for methyl methacrylate. This implies that the styrene radical is more reactive than the methyl methacrylate radical towards *p*-benzoquinone; study of co-polymerizing systems indicates that generally the methyl methacrylate radical is a little more reactive than the styrene radical.

It was shown (Bevington, Ghanem, and Melville, *loc. cit.*) that the radical $RO·C_6H_4·O·$, where R represents a poly(methyl methacrylate) chain, is comparatively unreactive. This ether radical has only a slight tendency to attack a molecule of monomer to give the new radical $RO·C_6H_4·O·CH_2·CMe·(CO_2Me)·$ which is able to engage in further growth reactions; the ether radical usually combines with an ordinary poly(methyl methacrylate) radical to give the molecule $RO·C_6H_4·OR$. The ether radical formed by the attack of a polystyrene radical on *p*-benzoquinone is able to add on a molecule of styrene rather more readily; this is shown by the fact that polymers formed during the induction periods contain on the average nearly two molecules of the quinone per polymer molecule. There is therefore a slight tendency for the quinone to co-polymerize with styrene. The conclusion that there is a greater tendency for *p*-benzoquinone to co-polymerize with styrene than with methyl methacrylate is in agreement with the accepted view that the styrene molecule is a little more reactive than the methyl methacrylate molecule.

The combination $2\ RO·C_6H_4·O· \longrightarrow RO·C_6H_4·O·O·C_6H_4·OR$ would lead to the inclusion of two quinone molecules in each polymer molecule; this combination seems rather unlikely, however, since the product is a peroxide. The most likely termination reaction in the early stages of the polymerization can be represented as $X·R·O·C_6H_4·O· + ·R'O·C_6H_4·OR''·X \longrightarrow X·R·O·C_6H_4·O·R'·O·C_6H_4·O·R''·X$ where R, R′, and R″ represent short polystyrene chains, and X represents an initiator fragment.

Conclusion.—The results in this paper show that the use of reagents labelled with ^{14}C can provide most valuable information about the mechanisms of complex organic reactions. Results can be obtained by using labelled reagents of quite moderate specific activity. It has been possible to determine accurately products of low molecular weight formed simultaneously with polymer even if the weights of these products are very considerably less than 1 mg. and the substances are present in complex mixtures. In investigating polymerizing systems, it is necessary to combine the isotopic methods with older methods of study, *e.g.*, determination of rates of reaction and of average molecular weights of polymers, in order to obtain a complete picture of the reaction.

It has been shown that when styrene is polymerized in the presence of *p*-benzoquinone, growth of the polymer radicals is stopped prematurely by interaction with the quinone. Most of the quinone becomes incorporated in polymer, but some of it reacts with radicals generated from the initiator to give products of low molecular weight. There is clear evidence that there is limited co-polymerization of styrene and *p*-benzoquinone. When the quinone is all consumed, the rate of polymerization rises to its normal value, and the

polymer then produced has the same molecular weight as a polymer prepared in the complete absence of *p*-benzoquinone with use of the same concentration of initiator. Additional evidence has been obtained that polymer radicals attack the molecule of *p*-benzoquinone at the oxygen atoms. It is shown that the use of labelled substances may assist materially in elucidating the mechanisms of reactions involving new organic reagents, *e.g.*, trifluoroacetic anhydride.

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Observations on the Ozonolysis of Allylic Compounds. The Structure of Geraniol.

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Geranyl acetate has been found to give less than 3% of formaldehyde on ozonolysis. It is concluded that the acetate and hence geraniol itself have predominantly the *iso*propylidene structure, in agreement with the infrared data. The ozonolysis of allylic compounds is discussed with reference to the general applicability of the Doeuvre–Naves method for the estimation of Δ^1-unsaturation.

THE infrared spectrometric studies of Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland (*J.*, **1950**, 915) and of Carrol, Mason, Thompson, and Wood (*ibid.*, p. 3457) have shown that simple acyclic terpenes such as geraniol (I) (for this and other formulæ see Table) and citronellol (II) exist predominantly, if not completely, in the *iso*propylidene form. This conclusion, which confirmed the interpretation of the Raman spectra by Naves, Brus, and Allard (*Compt. rend.*, **1935**, **200**, 1112), is not in agreement with evidence obtained by oxidative degradation (cf. Simonsen and Owen, " The Terpenes," Vol. I, Cambridge, **1947**) and has been criticized by Simonsen and Owen (*op. cit.*, Vol. III, 1952, p. 481) on the grounds that no parallel oxidation experiments were carried out. Naves (*Bull. Soc. chim. France*, **1951**, **18**, 506) compared the infrared and the ozonolytic method for the estimation of *iso*propenyl structures and obtained excellent agreement between them for citronellol, citronellal, citral, citronellic acid and its ethyl ester, rhodinol, farnesal, and farnesyl acetate, but not for the allylic alcohols, linaloöl (III), 6 : 7-dihydrolinaloöl, and nerolidol (IV). In order to complete the comparison we have measured the yields of formaldehyde obtained on ozonolysis of geraniol, geranyl acetate, and some related compounds.

In the determination of the structure of ethylenic compounds by ozonolysis the so-called " ozonide " is often degraded by either an oxidative or a reductive procedure, and the yields of fission products are usually considerably less than the theoretical (cf. Young, McKenzie, Webb, and Roberts, *J. Amer. Chem. Soc.*, **1946**, **68**, 293). For quantitative purposes it must then be assumed that the relative yields of the various fission products parallel the proportions of structural types present in the starting material. This is not very satisfactory but fortunately in the case of terminal ethylenic unsaturation formaldehyde is produced without the necessity of decomposing the " ozonide " chemically, and may be estimated directly. This forms the basis of the method originally proposed by Doeuvre (*Bull. Soc. chim. France*, **1936**, **3**, 612) and recently modified by Naves (*Helv. Chim. Acta*, 1949, **32**, 1151). This procedure involves treating the ozonized solution with Schiff's reagent in dilute hydrochloric acid (Denigès, *Compt. rend.*, 1910, **150**, 529). Formaldehyde gives a *stable* red colour with this reagent, whereas other aliphatic aldehydes do

not; acraldehyde and glyoxylic acid are reported to interfere (see Walker, " Formaldehyde," Reinhold Publ. Corpn., New York, 1944, p. 244). The results summarized in the Table were obtained by using the method as described by Naves, but with precautions taken to prevent over-ozonization.

Three samples of geraniol were obtained from different commercial sources and were purified as indicated on p. 2833; all three then exhibited infrared spectra similar to those reported by Barnard *et al.* and by Carrol *et al.* (*locc. cit.*). Two samples (*a* and *c*) showed weak absorption bands at 916 and 881 cm.$^{-1}$ which are conceivably attributable to the presence of not more than 2% of structures containing CH_2:CHR and CH_2:CR_2 end-groups respectively. On ozonolysis, however, both samples gave formaldehyde in about 20% yield. The other geraniol sample exhibited bands at 905 and 884 cm.$^{-1}$ and probably contained about 7% of *iso*propenyl-type structures; this sample gave formaldehyde in about 25% yield. Similarly 3-methylbut-2-enol (VII), prepared by lithium aluminium hydride reduction of 3-methylbut-2-enoic acid (VI), and containing less than 2% of

Summary of ozonolysis results

	CH_2O (%)	CH_2:CR_2 (%), detd. by infrared spectrum
CMe_2:CH·CH_2·CH_2·CMe:CH·CH_2·OH (I*a*)	19, 20, 21	<2
(I*b*)	23, 25·5, 26	~7
(I*c*)	20, 22·5, 24	<2
CMe_2:CH·CH_2·CH_2·CMe:CH·CH_2·OAc (V)	<3, <3	<2
CMe_2:CH·CH_2·CH_2·CHMe·CH_2·CH_2·OH (II) [a]	~5	4—5
CMe_2:CH·CO_2H (VI)	1·5, 2	—
CMe_2:CH·CH_2·OH (VII)	23, 23·5	<2
CMe_2:CH·CH_2·OAc (VIII)	3	—
CHMe:CH·CH_2·OH (XI)	12, 14	—
CHMe:CH·CHO (X)	2·5, 3·5	—
CMe_2:CH·CH(OH)·CH_3 (IX) [b]	7, 8·5	~5
CHMe:CH·CH(OH)·C_2H_5 (XII)	<2, <2	—
CMe_2:CH·CH_2·CH_2·CMe(OH)·CH:CH_2 (III) [a]	50—56	0
CMe_2:CH·CH_2·CH_2·CMe:CH·CH_2·CH_2·CMe(OH)·CH:CH_2 (IV) [a] ...	49—62	4—5
CH_2:CH·CH(OH)·C_2H_5 (XIII)	50·5, 60·5	—
CH_2:CH·CH(OH)·C_9H_{11} (XIV)	48, 52·5	>98 [c]
CH_2:CMe·CH_2Bu^t (XV)	99	>99

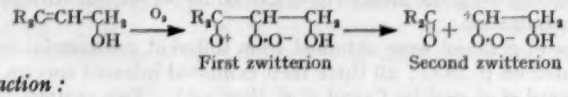
[a] Data from Naves (*Bull. Soc. chim. France*, 1951, **18**, 506). [b] The sample contained ~5% of 4-methylpenta-1 : 3-diene. [c] CH_2:CHR (%).

3-methylbut-3-enol according to its infrared spectrum, gave about 23% of formaldehyde. On the other hand, geranyl acetate (V) and 3-methylbut-2-enyl acetate (VIII), prepared from the alcohols by methods unlikely to give rise to allylic rearrangement, both gave less than 5% of formaldehyde. It is thus clear that geranyl acetate and hence geraniol itself must exist predominantly in the *iso*propylidene form and that geraniol, like other allylic alcohols (cf. Young *et al.*, *loc. cit.*), gives anomalous products on ozonization.

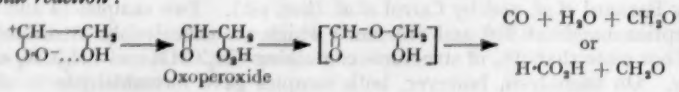
Mechanism of the Abnormal Ozonolysis.—Simonsen and Owen (*op. cit.*) suggested that large yields of formaldehyde or formic acid might be obtained from compounds such as geraniol if the *iso*propenyl and *iso*propylidene forms were in equilibrium, with the latter predominating but the former reacting more quickly with ozone. This explanation cannot be correct since the substitution of acetoxyl for hydroxyl should not affect the mobility or reactivity of such a system and yet the acetate gives very little formaldehyde on ozonolysis. Young *et al.* (*loc. cit.*) showed that ozone-catalysed, anionotropic rearrangements to linaloöl-type structures do not occur. They found that partial ozonolysis of crotyl alcohol or but-3-en-2-ol gives rise to abnormal products but that the recovered alcohol is not isomerized. This observation also indicates that prototropic rearrangements, *e.g.*, of crotyl alcohol to but-3-en-1-ol, do not occur.

Young *et al.* (*loc. cit.*) suggested that formaldehyde arises anomalously from an unexpected reaction of the " ozonide," and the mechanism which they proposed may be modified slightly, after the recent work of Criegee (*Fortschr. Chem. Forsch.*, 1950, **1**, 508). According to Criegee, addition of ozone to an ethylenic bond results in the formation of a zwitterion which splits to give a carbonyl compound and a second zwitterion.

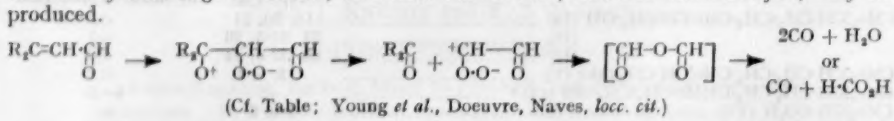
Normally the latter entity will polymerize or undergo reaction with the solvent, but if it contains a hydroxyl or oxo-group in the α-position it may undergo a rearrangement:



Abnormal reaction:

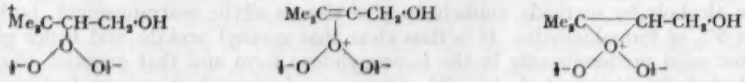


Young *et al.* found that allylic amines and ethers also undergo the abnormal ozonolysis but that esters do not. These workers suggested that in the presence of water the abnormal reaction might give rise to two molecules of formaldehyde, but this cannot be correct since a secondary alcohol such as 4-methylpent-3-en-2-ol, would then also give formaldehyde on ozonolysis, whereas in fact it does not. It will be obvious that for αβ-unsaturated aldehydes and ketones, the zwitterions themselves will be oxoperoxides which may rearrange as before, and that formic acid, but not formaldehyde, may be produced.

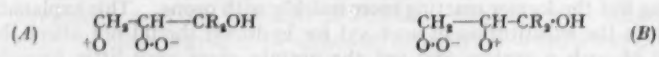


(Cf. Table; Young *et al.*, Doeuvre, Naves, *locc. cit.*)

It will be seen from the Table that the yields of formaldehyde are in the order: 3-methylbut-2-enol ~ geraniol > but-2-enol; and further, that for alcohols of linaloöl type (CH_2:$CH{\cdot}CR_2{\cdot}OH$), the yields are considerably lower than theoretical. It thus appears that substituent alkyl groups at the double bond affect the course of the ozonolysis. If the mechanism proposed above is correct, this must result from an alteration in the structure of the first zwitterion. Ozone is an electrophilic reagent (cf. Wibaut, Sixma, Kampschmidt, and Boer, *Rec. Trav. chim.*, 1950, **69**, 1355); hence it may not attack the carbon–carbon double bond in, for example, 3-methylbut-2-enol initially only at $C_{(2)}$, but probably forms a π-complex, as Badger (*ibid.*, 1952, **71**, 468) has suggested, or a three-membered ring intermediate ("ozonium ion") similar to that originally proposed by Roberts and Kimball (*J. Amer. Chem. Soc.*, 1937, **59**, 947) for halogen addition to ethylenic compounds:



Such intermediates would then rearrange to give either or both possible zwitterions, which in the case of an alcohol of the linaloöl type may be represented by (A) and (B). It will be seen that a zwitterion of type (*A*) can decompose to formaldehyde and may also undergo the



abnormal reaction (cf. Young *et al.*, *loc. cit.*) but that a zwitterion of type (*B*) cannot undergo the abnormal reaction; further, the products derived from $^+CH_2{\cdot}O{\cdot}O^-$ should not decompose to formaldehyde under the Doeuvre–Naves ozonolysis conditions. Hence, if the reaction proceeds at least partly *via* zwitterion (*B*), less than the theoretical yield of formaldehyde will be obtained. In allylic alcohols about equal amounts of the two structures must be formed (see Table), but in alk-1-enes, *e.g.*, 2 : 4 : 4-trimethylpent-1-ene, which give nearly theoretical yields of formaldehyde under these conditions, only the zwitterion of type (*A*) can be formed. This is at least in qualitative agreement with what might be expected by considering the relative charge distributions at $C_{(1)}$ and $C_{(2)}$ in the "ozonium ions" derived from such types of compounds.

The possible duality of reaction routes will affect the reliability of the Doeuvre–Naves method, but not procedures based on oxidative or reductive fission of the "ozonides." The former method is clearly trustworthy only when control experiments with model structures can be shown to give satisfactory results (cf. Adams, Wolff, Cain, and Clark, *J. Amer. Chem. Soc.*, **1940**, **62**, 2215; Karrer and Kebrle, *Helv. Chim. Acta*, **1952**, **35**, 862).

Experimental

Ozonolysis Technique.—Ozonized oxygen was passed through three tubes containing (i) the allylic compound (0·001—0·01 mole) in a 2 : 3 v/v mixture (5 ml.) of acetic acid and ethyl acetate at −20° to −10°, (ii) the solvent alone (2 ml.) at −20° to −10°, and (iii) potassium iodide in aqueous acetic acid. The iodine liberated in (iii) was titrated with standard sodium thiosulphate solution at intervals of one minute, ozonization being stopped when three successive titrations were the same to within ±0·1 ml. The contents of (i) and (ii) were treated with Schiff's reagent in dilute hydrochloric acid as described by Naves (*Helv. Chim. Acta*, **1949**, **32**, 1151), and the solution made up to 50 ml. and kept at 30° for exactly 2 hr. The amount of formaldehyde produced was determined with a Hilger "Spekker" colorimeter, a calibration curve being set up with standard formaldehyde solutions.

Infrared Spectra.—The spectra for pure liquid films were determined by Mr. R. L. Erskine using a Grubb–Parsons S 4 double-beam spectrometer with rock-salt optics. Estimates of the amounts of *iso*propenyl structures present were made from the intensity of the absorption band near 890 cm.$^{-1}$, a molecular extinction coefficient (ε) of 155 being assumed for a pure *iso*propenyl compound (cf. Barnard *et al.*, *loc. cit.*).

Geraniol (I).—(*a*) A sample obtained from L. Light and Co. Ltd. was converted into the calcium chloride adduct which was washed well with ether and *n*-hexane. Decomposition of the adduct with warm water followed by distillation gave geraniol, b. p. 118°/16 mm., n_D^{19} 1·4744, $[\alpha]_D^{20}$ 0·06° (Simonsen and Owen, *op. cit.*, give b. p. 229—230°/757 mm., 114—115°/12 mm., n_D^{20} 1·4766).

(*b*) A sample obtained from A. Boake Roberts and Co. Ltd. was purified as above; it had b. p. 74—74·5/1·0 mm., n_D^{19} 1·4710, $[\alpha]_D^{20}$ 0·00°.

(*c*) Another sample had b. p. 229—230°, n_D^{19} 1·4730, $[\alpha]_D^{20}$ 0·00°. The infrared spectra of samples (*a*) and (*c*) were very similar to those reported by Barnard *et al.* and Carrol *et al.* (*locc. cit.*) with the exception of a weak band due to a trace of a carbonyl compound (citral?) in (*a*) (cf. p. 2831).

Geranyl Acetate (V).—A mixture of geraniol (I*a*) (5 g.), acetic anhydride (5 g.), and pyridine (4 g.) was heated at 60—70° for 3 hr., then distilled, giving geranyl acetate (5 g.), b. p. 128—130°/21 mm., n_D^{19} 1·4590, $[\alpha]_D^{20}$ 0·00 (lit., b. p. 130—132°/22 mm., n_D^{15} 1·4620).

3-Methylbut-2-enoic Acid (VI).—This was prepared by oxidizing mesityl oxide with sodium hypochlorite solution (Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 448) and on redistillation had m. p. 69·5—70·5° (Vogel, *loc. cit.*, gives m. p. 68°).

3-Methylbut-2-enol (VII).—Reduction of the acid (VI) (10 g.) with lithium aluminium hydride (4·7 g.) in ether gave the alcohol (VII) (4·7 g.), b. p. 50—51°/13 mm., $n_D^{21\cdot5}$ 1·4385 (Braude and Timmons, *J.*, 1950, 2007, give b. p. 84—86°/80 mm., n_D^{20} 1·4382).

3-Methylbut-2-enyl Acetate (VIII).—The alcohol (VII) (1·0 g.), acetyl chloride (1·0 g.), and pyridine (5 ml.) were kept below 35° for 15 min. After being worked up in the usual manner, the acetate (VIII) (0·8 g.) had b. p. 148—149°, n_D^{22} 1·4245 (Courtot, *Bull. Soc. chim. France*, **1906**, **35**, 662, gives b. p. 149—150°, n_D^{25} 1·4233).

4-Methylpent-3-en-2-ol (IX).—Mesityl oxide (10 g.), on treatment with lithium aluminium hydride (2 g.) in ether, gave the alcohol (IX) (4 g.), b. p. 138—139°, n_D^{19} 1·4330 (Found: C, 72·1; H, 12·1. Calc. for $C_6H_{12}O$: C, 72·0; H, 12·1%). The infrared and ultraviolet spectra ($\lambda_{max.}$ 2260 Å, ε 1400, in EtOH) indicate the presence of ~5% of 4-methylpenta-1 : 3-diene.

Pent-1-en-3-ol (XIII).—Acraldehyde (5 g.) and ethylmagnesium bromide in ether yielded the product (XIII) (1·4 g.), b. p. 97·5—98·5°/50 mm., n_D^{18} 1·4238 (Delaby, *Compt. rend.*, 1922, **175**, 967, gives b. p. 114—116°, n_D^{27} 1·4182).

Hex-4-en-3-ol (XII).—Crotonaldehyde (5 g.) and ethylmagnesium bromide in ether gave the hexenol (2 g.), b. p. 129—130°, n_D^{19} 1·4318 (Auwers and Westerman, *Ber.*, 1921, **54**, 2993, give b. p. 135—135·5°, n_D^{25} 1·4325).

Oct-1-en-3-ol (XIV).—A commercial sample, when redistilled, had b. p. 174—175°, n_D^{19} 1·4369.

Crotonaldehyde (X).—The commercial product was redistilled and dried ($MgSO_4$); it had b. p. 103—103·5°, n_D^{19} 1·4322.

cis-*Crotyl Alcohol* (XI).—A sample prepared by semi-hydrogenation of but-2-ynol, for which we thank Dr. L. Crombie and Mr. C. K. Warren, had b. p. 63—64°/16 mm., n_D^{25} 1·4290.

2 : 4 : 4-*Trimethylpent*-1-*ene* (XV).—The sample used contained >99% of 2 : 4 : 4-trimethylpent-1-ene.

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Heterocyclic Systems Related to Pyrrocoline. Part I. 2 : 3a-*Diazaindene.*

By J. D. Bower and G. R. Ramage.

[Reprint Order No. 6422.]

2 : 3*a*-Diazaindene (I) and various derivatives have been prepared by the cyclisation of 2-1′-acylaminoalkylpyridines. Acetylation of 2 : 3*a*-diazaindenes under Friedel–Crafts conditions has been shown to occur at the 1-position or, when this position is blocked as in 1-methyl-2 : 3*a*-diazaindene, at the 3-position. This is the reverse of the order of substitution in pyrrocoline (II).

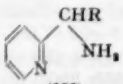
Although the chemistry of pyrrocoline (II) and its derivatives has been widely studied (Borrows and Holland, *Chem. Rev.*, 1948, **42**, 611) little is known about some of the nitrogen heterocyclic systems derived from pyrrocoline by replacement of the =CH– groups of the five-membered ring by nitrogen. Routes leading to such compounds have been examined and this paper is concerned with 2 : 3*a*-diazaindene (I) and some of its derivatives. Their preparation was achieved by the cyclisation of various 2-1′-acylaminoalkylpyridines by phosphoryl chloride.

2-Aminomethylpyridine (III; R = H) has been prepared by reduction of 2-cyanopyridine (Graf, *J. prakt. Chem.*, 1934, **140**, 39; 1936, **146**, 88; Kolloff and Hunter, *J. Amer. Chem. Soc.*, 1941, **63**, 490) but the reduction of pyridine-2-aldoxime (Craig and Hixon, *ibid.*, 1931, **53**, 4367) was found to be more satisfactory since commercial pyridine-2-aldehyde is now available.

1-Substituted 2 : 3*a*-diazaindenes were obtained from substituted 2-aminomethylpyridines. Two such amines (III; R = Me or Et) were prepared by the reduction of the

(I)

(II)



(III)

oximes of methyl and ethyl 2-pyridyl ketone and gave 1-methyl- and 1-ethyl-2 : 3*a*-diazaindene respectively.

Cyclisation of 2-formamidomethylpyridines gave 2 : 3*a*-diazaindenes which were unsubstituted at the 3-position, while substituents in this position were obtained by the use of acetyl, propionyl, and benzoyl derivatives of the amines. For example, 1-methyl-2 : 3*a*-diazaindene was obtained by cyclisation of the formyl derivative of the amine (III; R = Me) while the acetyl derivative of 2-1′-aminopropylpyridine (III; R = Et) gave 1-ethyl-3-methyl-2 : 3*a*-diazaindene. Compounds with substituents in the pyridine ring have not been prepared, but the route seems capable of extension in this way.

Attempts to prepare 2-acetamidomethylpyridine by acetylation with boiling acetic anhydride led to an oil which could not be purified, but when milder conditions were used (acetic acid and acetic anhydride at 100°) the acetyl derivative was readily obtained crystalline. It was found that acetic anhydride alone caused cyclisation together with some acetylation of the 3-methyl-2 : 3*a*-diazaindene formed.

The alkyl-substituted 2 : 3*a*-diazaindenes were obtained as liquids or low-melting solids which had a characteristic odour and darkened on storage, especially when impure. They were fluorescent under ultraviolet illumination, which was used to aid the chromatographic purification. Crystalline derivatives were formed with picric acid, methyl iodide, mercuric chloride, and silver nitrate, those with the last reagent having two molecules of the base associated with one of silver nitrate.

In view of the acetylation of 3-methyl-2 : 3*a*-diazaindene by acetic anhydride, the acetylation of the 2 : 3*a*-diazaindene system was studied under Friedel–Crafts conditions. The parent base (I) formed a monoacetyl derivative which was shown to be 1-acetyl-2 : 3*a*-diazaindene by Wolff–Kishner reduction to 1-ethyl-2 : 3*a*-diazaindene, which was also prepared by cyclisation of 2-1′-formamidopropylpyridine with phosphoryl chloride. 3-Methyl-2 : 3*a*-diazaindene was similarly shown to acetylate at the 1-position and gave the same acetyl derivative as was obtained by the action of acetic anhydride on 2-aminomethylpyridine and on 3-methyl-2 : 3*a*-diazaindene. However, 1-methyl-2 : 3*a*-diazaindene, in which the 1-position was blocked, was still acetylated, but at the 3-position. These results are in contrast with those obtained for the acetylation of pyrrocoline and its derivatives with acetic anhydride, which occurred preferentially at the 3-position and, when this was occupied, at the 1-position.

Experimental

2-Aminomethylpyridine.—This amine, b. p. 95—98°/20 mm., was prepared in 81% yield by reduction of pyridine-2-aldoxime with zinc powder and acetic acid (Craig and Hixon, *loc. cit.*). By the action of boiling 98% formic acid (6 c.c.) on the amine (2 g.) for 3 hr., *2-formamidomethylpyridine* was obtained as a pale yellow oil (1·95 g., 77%), b. p. 160—161°/4 mm. (Found : C, 61·9; H, 6·2; N, 21·0. $C_7H_8ON_2$ requires C, 61·7; H, 5·9; N, 20·6%). The *picrate* formed prisms, m. p. 158°, from benzene (Found : C, 43·2; H, 3·0. $C_7H_8ON_2,C_6H_3O_7N_3$ requires C, 42·7; H, 3·0%). The amine (3 g.) with acetic anhydride (5 c.c.) in acetic acid (15 c.c.) at 100° for 30 min. gave *2-acetamidomethylpyridine* as a pale yellow liquid (3·7 g., 89%), b. p. 160—163°/5 mm., which solidified, and crystallised from benzene–light petroleum (b. p. 60—80°) as plates, m. p. 59—60° (Found : C, 64·0; H, 6·8. $C_8H_{10}ON_2$ requires C, 64·0; H, 6·7%).

2 : 3a-*Diazaindene.*—2-Formamidomethylpyridine (1·95 g.) and phosphoryl chloride (4 c.c.) were heated under gentle reflux in benzene (12 c.c.) for 4 hr. The benzene and the excess of phosphoryl chloride were removed under reduced pressure and the residue was decomposed with water, basified, and extracted with chloroform. Fractionation of the dried extract gave the crude base (1·35 g., 80%), b. p. 120—125°/3 mm., which solidified and rapidly darkened. It was purified by evaporation at 80—90°/2 mm. on to a " cold finger " condenser, followed by chromatography on alumina in benzene containing 1% of methanol, and re-evaporation. 2 : 3a-*Diazaindene* was obtained as needles, m. p. 54—55°, having a strong light blue fluorescence under ultraviolet light (Found : C, 71·4; H, 5·2. $C_7H_6N_2$ requires C, 71·2; H, 5·1%). The *picrate* formed needles, m. p. 216° (decomp.), from ethanol (Found : C, 45·0; H, 3·0. $C_7H_6N_2,C_6H_3O_7N_3$ requires C, 45·0; H, 2·6%), and a *compound* with silver nitrate crystallised from water as needles, m. p. 178° (Found : C, 41·7; H, 2·9. $AgNO_3,2C_7H_6N_2$ requires C, 41·4; H, 3·0%).

1-*Acetyl*-2 : 3a-*diazaindene.*—2 : 3*a*-Diazaindene (0·83 g.) in carbon disulphide (15 c.c.) was added to a mixture of aluminium chloride (3·75 g.) and acetyl chloride (2·2 g.) in carbon disulphide (35 c.c.). The whole was stirred and boiled under reflux for 4 hr. and the solvent was removed by distillation from the water-bath. The residue was decomposed with ice-water, and an excess of sodium hydroxide solution (30%) was added before the resulting mixture was extracted with chloroform. Evaporation of the chloroform gave 1-*acetyl*-2 : 3a-*diazaindene* (0·8 g., 71%) which crystallised from *cyclo*hexane as cream needles, m. p. 129°, having a violet fluorescence in ultraviolet light (Found : C, 67·7; H, 5·0; N, 17·6. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%).

3-*Methyl*-2 : 3a-*diazaindene.*—2-Acetamidomethylpyridine (2·9 g.), by the phosphoryl chloride treatment, gave an oil (1·6 g., 62%), b. p. 112—117°/4 mm., which solidified but rapidly darkened and became oily again. Repeated crystallisation from *cyclo*hexane gave 3-*methyl*-2 : 3a-*diazaindene* as prisms, m. p. 55°, which had a blue fluorescence in ultraviolet light (Found : C, 72·2; H, 6·1. $C_8H_8N_2$ requires C, 72·7; H, 6·1%). The *picrate* was obtained as prisms, m. p. 221° (decomp.), after crystallisation from a large volume of ethanol (Found : C, 46·5; H,

3·2. $C_8H_8N_2,C_6H_3O_7N_3$ requires C, 46·5; H, 3·1%). Methyl iodide in boiling acetone formed a hydrated derivative which was dried at 100°/3 mm. and then gave the *methiodide*, m. p. 184° (Found : C, 38·9; H, 4·1. $C_9H_{11}N_2I$ requires C, 39·4; H, 4·0%). The *compound* with silver nitrate crystallised from water as needles, m. p. 189—190° (Found : C, 43·8; H, 3·6. $AgNO_3,2C_8H_8N_2$ requires C, 44·3; H, 3·7%).

1-*Acetyl*-3-*methyl*-2 : 3a-*diazaindene*.—(*a*) 3-Methyl-2 : 3*a*-diazaindene (0·9 g.) was acetylated with acetyl chloride (1·2 g.) and aluminium chloride (2·6 g.) in carbon disulphide (50 c.c.) as described above. Evaporation of the chloroform gave a dark residue which crystallised from benzene–light petroleum (b. p. 60—80°) as brown needles (0·9 g., 75%), m. p. 138°. Recrystallisation gave 1-*acetyl*-3-*methyl*-2 : 3a-*diazaindene* as fawn needles, m. p. 139°, having a violet fluorescence in ultraviolet light (Found : C, 69·3; H, 5·9. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·8%).

(*b*) 2-Aminomethylpyridine (1·2 g.) was boiled under reflux with acetic anhydride (5 c.c.) for 5 hr. Removal of the excess of acetic anhydride, treatment of the residue with water and alkali, chloroform extraction, and evaporation gave a solid. The product from the benzene extract of this crystallised from benzene–light petroleum (b. p. 60—80°) as yellow-brown needles (0·7 g., 36%), m. p. 136—138°. Recrystallisation gave fawn needles, identical with those obtained by method (*a*), m. p. and mixed m. p. 139°.

(*c*) 3-Methyl-2 : 3*a*-diazaindene (0·3 g.) was heated under reflux for 5 hr. with acetic anhydride (3 c.c.). A similar process to that used above gave a chloroform extract, the material from which was separated by chromatography into 3-methyl-2 : 3*a*-diazaindene (0·06 g.), identified as the methiodide, and 1-acetyl-3-methyl-2 : 3*a*-diazaindene (0·14 g.), m. p. 139°.

3-*Phenyl*-2 : 3a-*diazaindene*.—Cyclisation of 2-benzamidomethylpyridine (1·1 g.; Graf, *J. prakt. Chem.*, 1936, **146**, 88) gave a dark oil which, on evaporation at 140°/2 mm. on to a " cold finger " condenser followed by crystallisation from *cyclo*hexane, gave 3-*phenyl*-2 : 3a-*diazaindene* (0·62 g., 61%) as prisms, m. p. 109° (Found : C, 80·1; H, 5·2. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·2%). The *picrate* formed needles, m. p. 185—186°, from ethanol (Found : C, 53·9; H, 3·0. $C_{13}H_{10}N_2,C_6H_3O_7N_3$ requires C, 53·9; H, 3·1%).

2-1′-*Aminoethylpyridine*.—Methyl 2-pyridyl ketoxime, m. p. 120°, from methyl 2-pyridyl ketone (Gilman, Tolman, and Massie, *J. Amer. Chem. Soc.*, 1946, **68**, 2399) was reduced by the method used (above) for the preparation of 2-aminomethylpyridine and gave 2-1′-aminoethylpyridine (86%), b. p. 197—201°/760 mm. 2-1′-*Formamidoethylpyridine* (78%) was obtained as a pale yellow liquid, b. p. 156°/4 mm. (Found : C, 63·9; H, 7·0. $C_8H_{10}ON_2$ requires C, 64·0; H, 6·7%), and 2-1′-*acetamidoethylpyridine* crystallised from *cyclo*hexane as needles, m. p. 107° (Found : C, 66·2; H, 7·4. $C_9H_{12}ON_2$ requires C, 65·8; H, 7·4%). The action of propionic anhydride on the amine for 75 min. on the water-bath gave the propionyl derivative as an oil, b. p. 155—158°/5 mm., which formed deliquescent needles when cool. The *picrate* of 2-1′-propionamidoethylpyridine formed prisms, m. p. 128°, from benzene (Found : C, 47·2; H, 4·1. $C_{10}H_{14}ON_2,C_6H_3O_7N_3$ requires C, 47·2; H, 4·2%). Benzoylation of 2-1′-aminoethylpyridine by the Schotten–Baumann method gave 2-1′-*benzamidoethylpyridine* as needles, m. p. 93° [from light petroleum (b. p. 60—80°)] (Found : C, 74·9; H, 6·2. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%).

1-*Methyl*-2 : 3a-*diazaindene*.—2-1′-Formamidoethylpyridine with phosphoryl chloride gave a crude product (70%), b. p. 100—105°/1·5 mm. Redistillation, followed by chromatography on alumina in benzene containing 1% of methanol, and evaporation at 70°/3 mm. on to a " cold finger " condenser gave 1-*methyl*-2 : 3a-*diazaindene* as needles, m. p. 64—65° (Found : C, 72·7; H, 6·2. $C_8H_8N_2$ requires C, 72·7; H, 6·1%). The *methiodide* crystallised as needles, m. p. 209°, from acetone (Found : C, 39·2; H, 4·0. $C_9H_{11}N_2I$ requires C, 39·4; H, 4·0%).

1-Methyl-2 : 3*a*-diazaindene was acetylated by the Friedel–Crafts procedure and the product (88%) solidified to yellow needles, m. p. 54—56°. Crystallisation from light petroleum (b. p. 60—80°), evaporation at 100°/3 mm., and recrystallisation gave 3-*acetyl*-1-*methyl*-2 : 3a-*diazaindene* as pale yellow needles, m. p. 66—67° (Found : C, 69·0; H, 5·9. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·8%). The crystals had a violet fluorescence in ultraviolet light.

1 : 3-*Dimethyl*-2 : 3a-*diazaindene*.—Cyclisation of 2-1′-acetamidoethylpyridine (1·6 g.) gave 1 : 3-dimethyl-2 : 3a-diazaindene as a yellow oil (1·09 g., 76%), b. p. 120—125°/5 mm., which solidified to deliquescent prisms. The *picrate* formed plates, m. p. 254° (decomp.), on crystallisation from a large volume of ethanol (Found : C, 48·2; H, 3·5. $C_9H_{10}N_2,C_6H_3O_7N_3$ requires C, 48·0; H, 3·5%).

3-*Ethyl*-1-*methyl*-2 : 3a-*diazaindene*.—(*a*) 2-1′-Propionamidoethylpyridine was cyclised and

gave a yellow oil (89%), b. p. 118—124°/4 mm. Redistillation gave **3-*ethyl*-1-*methyl*-2 : 3a-*diazaindene*** as a yellow oil, b. p. 130°/5 mm. (Found : C, 74·9; H, 7·6. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·6%). The ***mercurichloride*** formed needles, m. p. 203—204° (decomp.), from ethanol (Found : C, 27·8; H, 2·9. $C_{10}H_{12}N_2,HgCl_2$ requires C, 27·8; H, 2·8%). The ***compound*** with silver nitrate, prepared from an aqueous suspension, formed needles, m. p. 175° (decomp.), from aqueous methanol (Found : C, 48·5; H, 5·2. $AgNO_3,2C_{10}H_{12}N_2$ requires C, 49·0; H, 4·9%).

(*b*) Wolff–Kishner reduction (cf. Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487). 3-Acetyl-1-methyl-2 : 3*a*-diazaindene (0·22 g.), potassium hydroxide (1·0 g.), 90% hydrazine hydrate (0·75 c.c.), and ethylene glycol (7·5 c.c.) were heated under reflux for 1 hr. The temperature of the mixture was raised to 190° by distillation and maintained for 5 hr. An insoluble red intermediate was formed, but this disappeared during the treatment. Water (15 c.c.) was added to the cooled solution which was then extracted with chloroform. The oil obtained on evaporation of the extract was chromatographed in benzene on alumina and then converted into a mercurichloride and a silver nitrate derivative (31% yield). These were crystallised from ethanol and aqueous methanol respectively, and were identical with the mercurichloride and silver nitrate derivative of 3-ethyl-1-methyl-2 : 3*a*-diazaindene.

1-*Methyl*-3-*phenyl*-2 : 3a-*diazaindene*.—2-1′-Benzamidoethylpyridine on cyclisation gave **1-*methyl*-3-*phenyl*-2 : 3a-*diazaindene***, which crystallised from aqueous methanol as cream needles, m. p. 120° (Found : C, 81·1; H, 5·8. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8%).

2-1′-*Aminopropylpyridine*.—Reduction of ethyl 2-pyridyl ketoxime (from ethyl 2-pyridyl ketone; Bertucat, *Compt. rend.*, 1951, **232**, 1758) by zinc and acetic acid gave a 92% yield of **2-1′-*aminopropylpyridine***, b. p. 110°/31 mm. (Found : C, 70·7; H, 9·0. $C_8H_{12}N_2$ requires C, 70·5; H, 8·9%). **2-1′-*Formamidopropylpyridine*** had b. p. 146°/2 mm. (Found : C, 65·8; H, 7·5. $C_9H_{12}ON_2$ requires C, 65·8; H, 7·4%), and **2-1′-*acetamidopropylpyridine*** was obtained as deliquescent prisms, m. p. 83° (Found : C, 67·3; H, 8·1. $C_{10}H_{14}ON_2$ requires C, 67·4; H, 7·9%).

1-*Ethyl*-2 : 3a-*diazaindene*.—(*a*) Cyclisation of 2-1′-formamidopropylpyridine (1·48 g.) gave **1-*ethyl*-2 : 3a-*diazaindene*** (1·12 g., 85%), b. p. 116°/2 mm., which darkened on storage (Found : C, 73·4; H, 7·2. $C_9H_{10}N_2$ requires C, 73·9; H, 6·9%). The ***picrate*** formed prisms, m. p. 203° (decomp.) (Found : C, 47·9; H, 3·5. $C_9H_{10}N_2,C_6H_3O_7N_3$ requires C, 48·0; H, 3·5%), and the ***picrolonate*** gave needles, m. p. 222° (Found : C, 55·6; H, 4·7. $C_9H_{10}N_2,C_{10}H_8O_5N_4$ requires C, 55·6; H, 4·4%), both from ethanol. A ***compound*** with silver nitrate was obtained as needles, m. p. 152—153°, from water (Found : C, 46·9; H, 4·4. $AgNO_3,2C_9H_{10}N_2$ requires C, 46·8; H, 4·4%).

(*b*) Reduction of 1-acetyl-2 : 3*a*-diazaindene (0·22 g.) by the modified Wolff–Kishner method gave an oil which was converted into a picrate, picrolonate, and a compound with silver nitrate, which were identical with the corresponding derivatives obtained as above.

1-*Ethyl*-3-*methyl*-2 : 3a-*diazaindene*.—(*a*) 2-1′-Acetamidopropylpyridine gave **1-*ethyl*-3-*methyl*-2 : 3a-*diazaindene*** (80%), b. p. 115—123°/2 mm., which when redistilled had b. p. 120°/2 mm. (Found : C, 75·3; H, 7·7. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·6%). The ***mercurichloride*** formed diamond-shaped plates, m. p. 210—211° (decomp.), from ethanol (Found : C, 28·3; H, 3·2. $C_{10}H_{12}N_2,HgCl_2$ requires C, 27·8; H, 2·8%). The ***methiodide*** formed needles, m. p. 200°, from acetone (Found : C, 43·6; H, 5·0. $C_{11}H_{15}N_2I$ requires C, 43·7; H, 5·0%), and the ***picrate*** was obtained as diamond-shaped plates, m. p. 259° (decomp.), from ethanol (Found : C, 49·4; H, 3·8. $C_{10}H_{12}N_2,C_6H_3O_7N_3$ requires C, 49·4; H, 3·9%).

(*b*) Reduction of 1-acetyl-3-methyl-2 : 3*a*-diazaindene. The modified Wolff–Kishner procedure used above gave an oil which, after chromatography, was converted into a picrate and a mercurichloride (yield 33%). The former had m. p. 258—259°, not depressed on admixture with the picrate of 1-ethyl-3-methyl-2 : 3*a*-diazaindene, and the latter, m. p. 210—211°, was identical with the corresponding mercurichloride.

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Exchange Equilibria in Crystals of Chabazite.

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Exchange equilibria between aqueous solutions and crystals of chabazite have been studied quantitatively for the ion pairs Na–Cu, Na–Ag, Na–Tl, Na–Rb, Na–Ca, Na–Ba, and K–Ag. In all cases the pure chabazite salts formed continuous series of solid solutions. Equilibria were reached reversibly and were nearly independent of temperature within the ranges studied. The Na–Ag exchange was nearly ideal in as far as the simple law of mass action was valid. The other uni-univalent exchange equilibria were satisfactorily represented by the relation

$$\log K = \log \frac{B_z(1 - B_s)}{B_s(1 - B_z)} + C(1 - 2B_z)$$

where K and C are constants and B_z, B_s are the equivalent cation fractions of ionic species B in zeolite and in solution respectively. A number of these isotherms were sigmoid. Some of them have been subjected to thermodynamic analysis.

Chabazite samples rich in H, Li, Mg, Sr, NH_4, Co^{2+}, Ni^{2+}, and Pb^{2+} were also prepared. Attempts to prepare La^{3+}-, NMe_4-, and NEt_4-rich forms were unsuccessful in the case of the organic ions on account of an ion-sieve effect. Properties of various pure chabazite salts have been determined, such as refractive indices, water content, X-ray diffraction patterns, and unit cells. The unit cell of chabazite is changed very little by ion exchange.

In crystalline media ion exchange may be considered a type of solid-state reaction. There are many crystalline aluminosilicates in which ion exchange occurs freely, notably some members of the clay-minerals group, the zeolite group, and the felspathoids. The clays, although widely studied from this viewpoint, do not lend themselves well to investigations of ion exchange as a solid-state reaction. The crystals are small and often imperfect, and the exchange may be accompanied by extensive swelling and shrinking along the c-axis. By contrast with these layer-lattice minerals, the felspathoids and many of the zeolites are excellently crystalline with robust three-dimensional network structures, permeated by intersecting or interconnected channels of molecular dimensions. In such media one may seek for an exchanger which is "ideal" from the theoretical viewpoint: this means a crystal in which the anionic framework forms a wholly inert, unchanging, and charged structure, into which cations A may be inserted with the displacement of an electrochemical equivalent of cations B. Barrer (Colloq. Internat., "Reactions dans l'État Solide," C.N.R.S., Paris, 1948) assumed each ion to go on to definite sites, and from statistical considerations evaluated the equilibrium constants for the reactions

$$AX_{(s)} + BZ_{(s)} \longrightarrow BX_{(s)} + AZ_{(s)} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where X is an anion (Cl^-, NO_3^-, etc.) and Z denotes the zeolitic framework. It was considered that BZ and AZ were in solid solution with each other (these solid solutions being ideal in accordance with the above definition of the ideal exchanger). Cases were considered where each salt AX and BX was in equilibrium with its saturated aqueous solution and the zeolite crystals, where the ion-exchanging medium was and was not hydrated, and where the water content did and did not change during the process of exchange. Systems were also considered where AX and BX formed a mixed ionic melt or were in unsaturated aqueous solution together. The zeolites represent typical hydrated crystals while the felspathoids are anhydrous.

Investigations have now been made of ion-exchange processes in analcite, mordenite, and chabazite (Barrer, *J.*, 1948, 2158; *J.*, 1950, 2342). Quantitative studies of ion-exchange diffusion kinetics and equilibria have been made in the zeolites analcite (Barrer

and Hinds, *J.*, **1953**, 1879; Barrer and Falconer, unpublished work), chabazite (this paper), and faujasite (Barrer, Buser, and Grutter, unpublished work); and in the felspathoids ultramarine (Barrer and Raitt, *J.*, **1954**, 4641) and cancrinite (Barrer and Falconer, unpublished work). It has been clearly established that analcite is not an ideal exchanger in the sense given by Barrer (*loc. cit.*). The framework does participate in the exchange process, and where the exchanging cation pairs differ appreciably in ion size the exchange isotherms may exhibit discontinuities due to limited mutual solid solubility of the end members, pure AZ and pure BZ. Associated with this behaviour there arises hysteresis due to the difficulty of nucleating one solid phase in or on another (Barrer and Hinds, *loc. cit.*; Thomas and Staveley, *J.*, **1951**, 2572; Barrer, Drake, and Whittam, *Proc. Roy. Soc.*, **1953**, *A*, **219**, 32). Ultramarine also may sometimes exhibit continuous and sometimes discontinuous solid solubility (Barrer and Raitt, *loc. cit.*).

For more open structures (mordenite, chabazite, faujasite) one may enquire whether the behaviour will be more ideal, and in particular whether the end members will exhibit continuous solid solubility. The anionic frameworks here include cages fully large enough to contain without strain either of two ions of widely differing sizes. However, difficulties may still arise over valency differences between ions (*e.g.*, $2Na^+ \rightleftharpoons Ca^{2+}$) and local balance of anionic charge; and also the ion size and polarisability may influence the equilibrium constants substantially. We present in this paper an investigation of ion-exchange equilibria in chabazite and their interpretation.

Experimental

Naturally occurring chabazite crystals from the Bay of Fundy, Nova Scotia, were detached, as interpenetrating clusters, from their rock matrices, and separated from intergrown stilbite and calcite. The crystals were ground and in nearly all the quantitative work the portion between 120 and 200 mesh was used. The methods of exchange employed involved heating the crystals with salt solutions [LiCl, NaCl, KCl, RbCl, CsCl, $MgCl_2$, $SrCl_2$, $BaCl_2$, $AgNO_3$, $TlNO_3$, NH_4Cl, $CuSO_4$, $CuCl_2$, $NiCl_2$, $Pb(NO_3)_2$, $La(NO_3)_3$, NMe_4Br, NEt_4I], heating with fused salts ($NaClO_4$, $AgNO_3$), or heating in presence of vaporised salt (NH_4Cl).

Exchanging salts were, except where otherwise stated, of " AnalaR " grade; rubidium and cæsium chlorides of 99·9% purity were supplied by Johnson, Matthey Ltd.; thallium nitrate from B.D.H. was recrystallised once from water, filtered off, washed with water, and vacuum-dried before use. Distilled water was produced in a tin-plated copper still and gave a residue on evaporation of about 0·5 mg. per 100 ml. This residue contained copper. For some experiments de-ionised water was used.

Most of the quantitative exchange reactions were carried out in sealed Pyrex-glass tubes. The lengths of tubing before use were extracted in boiling distilled water for about 5 hr. to remove any soluble material from the glass. To permit exchanger and solution to react at constant temperature and to keep mixing them, the sealed tubes were secured to rotating carriers in water or air thermostats. Water thermostats were used up to 45°, and air thermostats at higher temperatures up to 120°.

Chabazite was analysed by methods which are essentially those given by Groves (" Silicate Analysis," Allen and Unwin, London). The means of three analyses of the original natural chabazite, and of two analyses of Ca-chabazite formed by exchange of Na by Ca in the natural crystals are given in Table 1. The crystals are thus rich in Ca in the natural state and also higher in silica than the " ideal " formula with $SiO_2 : Al_2O_3 = 4 : 1$. It is known, however, that

Table 1. *Analyses of chabazite.*

	Natural chabazite Composition :		Ca-Chabazite Composition :	
	%	Molar	%	Molar
SiO_2	50·08	4·87	50·03	4·82
Al_2O_3	17·44	1·00	17·70	1·00
CaO	8·76	0·913	9·96	1·023
Na_2O	1·14	0·107	—	—
H_2O	21·90	7·10	22·16	7·08
Total	99·32	—	99·85	—

this ratio may vary rather widely in chabazite (*e.g.*, Wyart, *Bull. Soc. franç. Miner.*, 1933, **56**, 103). The ratio Al_2O_3/(Total Bases) is 0·981 and 0·978 in natural and in Ca-chabazite, respectively.

In quantitative analyses for other cations, standard methods were used where possible. Silver was estimated as silver chloride; lead and barium as chromate, and also as sulphate; calcium as $CaC_2O_4.H_2O$; copper as thiocyanate; thallium as iodide (precipitated at 0°) and also as chromate. Mixtures of rubidium and sodium chlorides were determined as follows. The solution was evaporated to dryness in a platinum dish and weighed. A blank correction was made for solids extracted from the wall of the reaction tube and present in the distilled water (*loc. cit.*). The chloride content of the solution was known since pipetted volumes of rubidium and sodium chlorides of known concentrations (N/4) were mixed. Accordingly, from the weight of mixed chlorides and the weight of Cl the Na and Rb may be found. The same procedure was used with cæsium and sodium chloride mixtures.

X-Ray examination of exchange products was made by using a Hilger HRX *X*-ray unit, with 9-cm. powder cameras. Filtered Cu-K_α radiation was used. Optical examination was carried out with a Leitz research microscope. Refractive indices were measured approximately by the Becke line method, using immersion liquids for which refractive indices had been determined by using an Abbé refractometer. When liquids with refractive indices just above and just below that of the crystals had been found, these liquids were mixed in different proportions until the crystals were no longer visible when immersed in the liquid. The refractive index of this liquid was then found with the Abbé refractometer, and taken as equal to that of the crystals.

Results.—Samples of chabazite were prepared which were rich in the following cations : Li, Na, K, Rb, and Cs; Mg, Ca, Sr, and Ba; Ag, Tl, NH_4, Cu^{II}, Co^{II}, Ni^{II}, and Pb^{II}. Attempts to produce chabazites rich in La^{III}, NMe_4, and NEt_4 were unsuccessful, the failure being ascribed to valency * in the case of La^{III}, and being due to an ion-sieve action with the very large tetra-alkylammonium ions. Among small uni- and bi-valent ions, however, there was free exchange with no obvious critical factor.

Exchanges giving crystals rich in Li, Na, K, Rb, and Cs were effected hydrothermally at 110°, 95°, 95°, 85°, and 25°, respectively. The starting materials were Ca- and natural chabazites respectively (Table 1); and the exchange reactions were followed by observations of weight change in the crystals, or of the calcium displaced. Na-Chabazite was also prepared by heating natural chabazite with fused sodium perchlorate. In agreement with an earlier study (Barrer, *J.*, 1950, 2342) magnesium could not be introduced directly into natural chabazite heated with saturated aqueous magnesium chloride at 85°. However, magnesium was introduced successfully at 95° by the reaction

$$MgCl_2(\text{sat.}) + 2AgCh \longrightarrow MgCh_2 + 2AgCl(s.)$$

where Ch denotes the anionic framework of chabazite. Calcium, strontium, and barium were introduced at 75°, 95°, and 85° and by use of Na-, natural, and Na-chabazite, respectively. The reactions were followed by weight change, or from changing compositions of the exchanging solutions, or both.

Silver-rich chabazites were readily made hydrothermally. There was, however, a tendency for grey or even darker products to appear, owing to the deposition of small amounts of metallic silver. This was so particularly with >0·5N-silver nitrate solutions. It was not possible to settle definitely the conditions giving metallic silver, but this deposition was negligible with concentrations ≯N/4, temperatures ≯45°, and times of experiment ≯24 hr. Heating chabazite crystals in fused silver nitrate gave a buff-coloured product, with extensive exchange. The colour indicates that this method does not eliminate a small silver deposition.

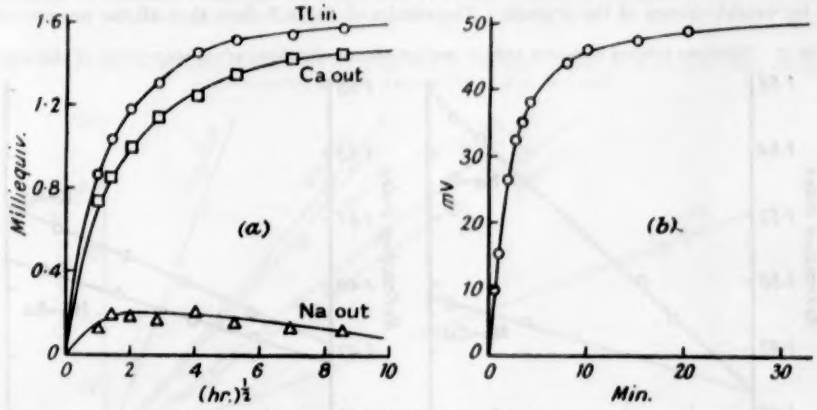
Thallium-rich chabazites were easily made hydrothermally, and extensive exchange of calcium for ammonium was also observed when ammonium chloride vapour at 350° was the exchange medium, or when ammonium chloride solution at 95° was used (cf. Barrer, *J.*, 1950, 2342). When chabazite crystals were heated with aqueous nickel chloride or copper sulphate at 110°, basic salts were formed, and the Cu-rich chabazite crystals were bluish. These crystals became deep blue on exposure to gaseous ammonia, while the nickel-rich crystals became pale violet. Treatment of pink chabazite with aqueous cobalt chloride at 110° gave a Co-rich

* In an exchange such as $3Na^+ \rightleftharpoons La^{3+}$, there may be local excess of positive charge at the site occupied by La^{3+}, and local excess of anionic charge at the sites vacated by two of the Na^+ ions. This disbalance may be unfavourable for exchange. At the same time it is evidently not a serious factor in the exchange $2Na^+ \rightleftharpoons Ca^{2+}$, and others of similar type.

chabazite in which the original pink hue was definitely deepened. The colour reactions of these three exchange products are evidently those normally associated with the cations in co-ordination with water or with ammonia. Finally, with lead nitrate solution at 95°, a considerable exchange $Pb^{2+} \rightleftharpoons Ca^{2+}$ was found in the chabazite, while on the other hand with lanthanum nitrate solution at 95° there was no change in weight in the crystals.

Hydrogen-ion Exchange.—When Ag-chabazite was heated with aqueous tetramethylammonium bromide at 95°, silver bromide was formed, which was removed by means of aqueous ammonia. The chabazite was then paler than originally. A similar treatment of Ca chabazite with the bromide gave no reaction; while treatment of the Ag-form with aqueous tetraethylammonium iodide at 95° gave silver iodide. This behaviour was comparable with that observed

FIG. 1.



(a) *Kinetics of exchange of* Tl^+ *for* $Ca^{2+} + Na^+$.
(b) E.M.F. *as a function of time in the exchange of* Ag^+ *for* Na^+.

earlier in Ag-ultramarine, Ag-analacite, and other species (Barrer and Raitt, *loc. cit.*; Barrer and Sammon, unpublished work). It was there shown to be due to hydrogen-ion exchange: $NMe_4Br + AgCh + H_2O \longrightarrow HCh + AgBr + NMe_4OH$. No alkylammonium ion is removed in this process, and the reaction depends wholly upon the inability of so large an ion to penetrate the crystals, and the insolubility of the silver halide.

Rates of Exchange.—Experiments were conducted to find the equilibration times for exchanges in chabazite. The ground, unsieved mineral (0·5 g.) was heated with 10 ml. of

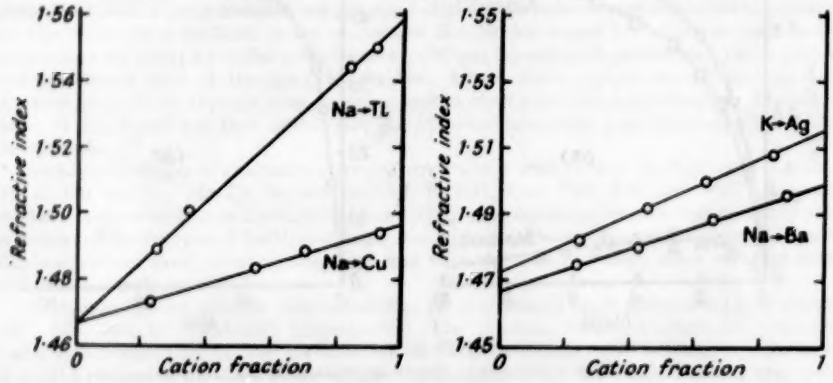
TABLE 2.

Exchanging solution, and method of analysis	Time (hr.)	Temp.	Exchange (%) By wt. of crystals	By analysis	Mean
$AgNO_3$; Ag detd. as AgCl	½	25°	97·7	97·5	97·6
	2	25	96·7	97·8	97·3
	5	25	97·2	97·1	97·2
$BaCl_2$; Ba detd. as $BaSO_4$	½	25	40·5	36·5	38·5
	2	25	66·1	63·0	64·6
	24	25	88·9	89·9	89·4
	½	85	37·7	37·9	37·8
	2	85	66·7	63·6	65·2
	4	85	90·9	93·8	92·4
	∞	85	88·3	92·1	90·2
CsCl; Cs detd. from wt. of evaporate	½	25	40·7	42·5	41·6
	2	25	60·9	56·9	58·9
	4	25	63·0	63·0	63·0
	∞	25	62·4	62·8	62·6
RbCl	½	85	88·2	—	88·2
	2	85	90·0	—	90·0
$TlNO_3$; Tl detd. as Tl_2CrO_4	½	25	98·8	100·0	99·4
	2	25	98·5	99·5	99·0

0·3036N-thallous nitrate in sealed tubes at 75°; thallium and calcium were determined for various intervals of time, and sodium was found by difference, with the results presented in Fig. 1*a*. The slight maximum in the amount of displaced sodium was attributed to the greater velocity with which univalent ions can be displaced when compared with bivalent ones (see below). Thus, initially, the thallium displaced more than the final equilibrium content of sodium, but at a later stage more of the less rapidly displaced calcium had diffused from crystals to solution, a little sodium re-entered the crystals, and a three-fold equilibrium was established within the crystals involving the species Tl^+, Na^+, and Ca^{2+}.

The presence of calcium was then eliminated, by using the pure Na-form of chabazite as exchanger, and treating this at 95° with a solution saturated with respect to both sodium sulphate and thallous sulphate. Reaction was then virtually complete in 75 min. Further experiments using 0·1 g. of Na-chabazite and 5 ml. of N/4-salt solutions were followed by analysis and by weight change of the crystals. The results of Table 2 show that all the uni-univalent

FIG. 2. *Relations between refractive indices and cationic compositions of exchange forms of chabazite.*



exchanges are very rapidly completed, whatever the ionic radius of the entering ions, even the sodium–cæsium exchange being effectively finished in 2 hr. By contrast with this the uni-bivalent exchange ($2Na \rightleftharpoons Ba$) requires a substantially longer time, even at 85°. Valency differences are evidently more important in determining the exchange kinetics than are ionic radii.

The high velocity of exchange renders the analytical method of following the kinetics unsuitable for measurements of exchange diffusion coefficients. An e.m.f. method is, however, possible. The cell

Ag	$AgNO_3$	satd. NH_4NO_3 in agar	$AgNO_3$ + stirred Na-chabazite + $NaNO_3$ powder	Ag

was studied at room temperature, and the e.m.f. measured continuously as a function of time (Fig. 1*b*). The high velocity of exchange was confirmed, and, suitably interpreted, the method may give exchange diffusion coefficients. In the present paper, however, the emphasis will be on exchange equilibria.

Properties of Cationic Forms.—(a) *Refractive indices.* The refractive indices of crystals of various intermediate cationic compositions were determined for the exchanges Na–Tl, Na–Cu, Na–Ba, and K–Ag. All the crystals had reacted to equilibrium with the ambient solutions and were of uniform refractive index throughout. All the refractive indices measured were mean values, since the crystals, being rhombohedral, have two such indices. In Fig. 2 are shown the indices as functions of cationic compositions of the mixed crystals. There is in every instance a linear relation, so that optical methods of analysis of these crystals are possible. There were, moreover, no immiscibility gaps between homoionic exchange forms of chabazite, since all crystals in any given sample, whatever the cationic compositions, had the same refractive index. Those of the pure ionic forms of chabazite are given in Table 3. Three factors influence the trend in the refractive index among cationic forms : the mass of the cations, their valency, and the extent to which the hydration changes in a given sequence of ions. Among alkali-metal

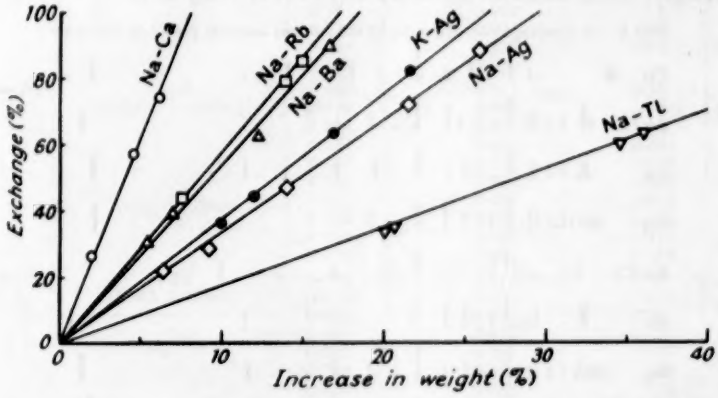
ions, the Li-form of chabazite is very highly hydrated, and this more than offsets the greater mass of the sodium ion. Among the alkali-metal cationic forms falling degree of hydration (see below) tends to balance increasing cationic mass.

TABLE 3. *Mean refractive indices of pure ionic forms of chabazite.*

Ionic form	n	Ionic form	n	Ionic form	n
Li	1·472	Ca	1·486	Cu	1·497
Na	1·467	Sr	1·490	Ag	1·516
K	1·472	Ba	1·499	Tl	1·559
Rb	1·476	—	—	—	—

(b) *Water content and cationic compositions.* The water contents of chabazite crystals were determined by ignition, except for Cu-, Ag-, and Tl-forms. In these and other cases the weight varies linearly as a function of changing cationic compositions (Fig. 3), and the linear graphs

FIG. 3. *Linear correlations between % exchange and % increases in weight of crystals, from which water contents of pure cationic forms may be found.*



serve to give the weight increases for 100% exchange. The results normally correspond to changes in water content in going from one pure cationic form to another (Table 4). In general, bivalent ions in chabazite produce a more highly hydrated condition than do univalent ones. Among the alkali-metal ions the water content of the crystals falls with increasing ionic radius, but for the bivalent alkaline-earth metal ions this trend does not appear. The results given in Table 4 may depend to some extent upon the relative pressure of water vapour, according to the degree of rectangularity of the sorption isotherms.

TABLE 4.

Cationic form	Water content: %	Water content: H_2O / MO (or M_2O)	Cationic form	Water content: %	Water content: H_2O / MO (or M_2O)
Li	21·8	6·5	Ca	22·1$_6$	6·9
Na	20·3	6·4	Sr	20·7	7·0
K	17·0$_8$	5·7	Ba	19·3	7·1
Rb	13·6	5·2	Cu	23·3	7·6
Tl	9·2	4·8	Ag	15·7	6·4

(c) *X-Ray spacings and unit cells of exchange forms.* The tabulated *X*-ray *d*-spacings of the various exchange forms showed that these spacings changed but little with different cations, although the relative intensities of the corresponding diffraction arcs show the expected changes (Fig. 4). The anionic framework of chabazite is therefore little altered by ion exchange. To support this conclusion quantitatively the *d*-spacings of Na-, Ag-, Ca-, and Ba-chabazite were indexed, calculated and measured *d*-spacings were compared, and the lengths of the rhombohedral unit cells and their angles were determined. To do this the hexagonal unit cells were

first determined, by using the appropriate logarithmic Bjurstrom diagram. The unit cells are given in Table 5. The calculated volumes of these cells for Na-, Ag-, Ca-, and Ba-chabazite are respectively 850, 836, 833, and 843 Å^3. The mean volume is 840 Å^3, and the maximum deviation from the mean is little more than 1%. The relative constancy of the unit-cell dimensions and

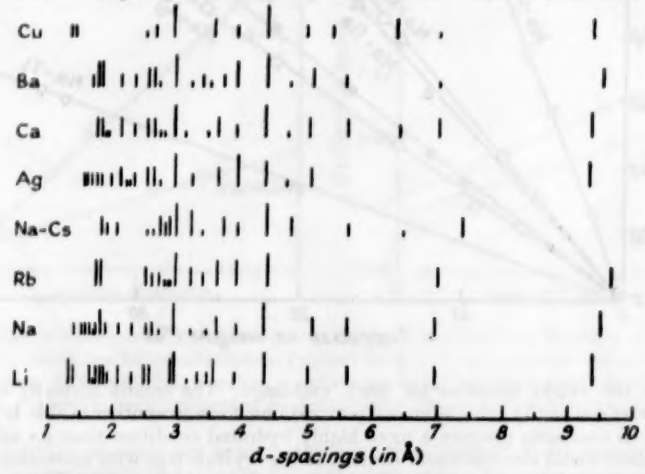
TABLE 5. *Hexagonal and rhombic unit cells of cationic forms of chabazite.*

Exchange	Hexagonal unit cells			Rhombic unit cells	
form	c (Å)	a (Å)	c/a	a (Å)	Angle
Na	$15{\cdot}2_5$	$13{\cdot}9_0$	1·097	$9{\cdot}5_9$	94° 3′
Ag	$15{\cdot}1_0$	$13{\cdot}8_6$	1·089	$9{\cdot}4_5$	94° 18′
Ca	$15{\cdot}0_0$	$13{\cdot}8_5$	1·083	$9{\cdot}4_3$	94° 27′
Ba	$15{\cdot}2_0$	$13{\cdot}8_6$	1·097	$9{\cdot}4_7$	94° 3′

d-spacings supports the view that chabazite approximates quite closely to the ideal crystalline exchanger in the sense discussed on p. 2838.

Exchange Isotherms.—Equilibrium isotherms were determined for the ion pairs Na–Ag, Na–Tl, Na–Rb, Na–Ca, Na–Cu, and Na–Ba. Typical isotherm contours are given in Figs. 5 and 6, and some numerical data are shown in Tables 6 and 7. Only for the Na ⟶ Ag exchange

FIG. 4. d-*Spacings characteristic of the various cationic forms of chabazite.*



are the mass-action quotients at all constant, emphasising the need for reformulating these quotients in terms of activities (see p. 2848). Sodium and silver ions, each having the same valency and rather similar ionic radii, give a mass-action quotient close to the thermodynamic equilibrium constant (Table 8). The uni-bivalent ion interchange, $2Na^+ \rightleftharpoons Ca^{2+}$, is of interest in that up to about two-thirds replacement of the sodium the equilibrium favours enrichment of the crystals in calcium at the expense of sodium. Thereafter the situation is sharply reversed. This may mean that the favoured cationic compositions of chabazite in Nature will tend to lie between 60 and 80% exchange to calcium. Such cationic compositions are indeed frequently observed. It may also mean that two-thirds of the sites in Na-chabazite differ in some way from the remaining third.

The continuous lines for uni-bivalent exchanges are smoothed curves on or near which the experimental points lie. For the uni-univalent exchanges these lines represent the best fit of the equation

$$\log K' = \log \frac{B_z(1 - B_s)}{B_s(1 - B_z)} + C(1 - 2B_z) \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Here K' and C are constants, the values of which are given on the Figs. 5 and 6; B_z and B_s are the equivalent ion fractions of the cation species B in the zeolite and in solution respectively. The ion fractions of the other cations are A_z and A_s; and in each phase $A_z + B_z = 1 = A_s + B_s$. Equation (2) can be given a semi-empircal interpretation as follows.

TABLE 6. *Uni-univalent exchanges in chabazite.*

System and temp.	Total normality of mixed electrolyte	Equiv. ion fraction in solution *	Equiv. ion fraction in zeolite	Mass-action quotient
Na ⟶ Ag (45°)	0·25 ($AgNO_3$ + $NaNO_3$)	0·020 (Ag_s)	0·224 (Ag_z)	14·2 $\left(\frac{Ag_zNa_s}{Ag_sNa_z}\right)$
		0·035	0·303	11·9
		0·076	0·476	11·0
		0·196	0·727	10·9
		0·275	0·809	11·2
		0·387	0·868	10·4
		0·468	0·882	11·8
		0·594	0·917	7·6
		0·796	0·976	10·4
Na ⟶ Ag (25°)	0·25 ($AgNO_3$ + $NaNO_3$)	0·025 (Ag_s)	0·297 (Ag_z)	16·3 $\left(\frac{Ag_zNa_s}{Ag_sNa_z}\right)$
		0·078	0·491	11·3
		0·103	0·597	12·9
		0·423	0·876	9·6
		0·538	0·900	7·7
		0·666	0·974	18·8
		0·727	0·973	13·6
		0·727	0·971	12·6
		0·728	0·972	13·0
		0·840	0·995	—
K ⟶ Ag (25°)	0·25 ($AgNO_3$ + KNO_3)	0·050 (Ag_s)	0·111 (Ag_z)	2·37 $\left(\frac{Ag_zK_s}{Ag_sK_z}\right)$
		0·179	0·243	5·14
		0·328	0·378	1·25
		0·484	0·450	0·874
		0·677	0·606	0·734
		0·680	0·593	0·686
		0·725	0·632	0·651
		0·854	0·760	0·543
		0·880	0·840	0·713
		0·930	0·860	0·465
Na ⟶ Rb (85°)	0·25 (RbCl + NaCl)	0·054 (Rb_s)	0·414 (Rb_z)	12·3 $\left(\frac{Rb_zNa_s}{Rb_sNa_z}\right)$
		0·075	0·438	9·65
		0·080	0·521	12·4
		0·128	0·610	10·7
		0·547	0·795	3·21
		0·742	0·824	1·63
		0·830	0·860	1·26
		0·870	0·913	1·56

* The equivalent on fraction of silver is $\frac{\text{silver normality}}{\text{total normality}}$.

In an aluminosilicate crystal wherein the anionic framework does not swell or shrink, and provided the water content of the framework does not alter perceptibly during exchange, one has at equilibrium for uni-univalent interchanges:

$$K = \frac{a_{B_z}a_{A_s}}{a_{B_s}a_{A_z}} = \frac{B_z(1-B_s)}{B_s(1-B_z)} \cdot \frac{f_{B_z}f_{A_s}}{f_{B_s}f_{A_z}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Here a's and f's are respectively activities and activity coefficients of the cations in the zeolitic or aqueous phases. However, the exchange isotherms were all determined in solutions of *constant* total normality in which only the *ratios* of A_s and B_s were changed. In this case the simplified form of Glueckauf's equation (*Nature*, 1949, **163**, 414) gives

$$\log \frac{f^{AX}_{(BX)}}{f^{BX}_{(AX)}} = \tfrac{1}{2} \log \frac{f^{AX}}{f^{BX}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Here $f^{AX}_{(BX)}$ is the activity coefficient of electrolyte AX in solution with BX of the given total molarity, and f^{AX} is the activity coefficient of AX at the same molarity in absence of BX. Also, since

$$f_{A_s}/f_{B_s} = \left[f^{AX}_{(BX)}/f^{BX}_{(AX)}\right]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

one may combine (4) and (5) and obtain

$$f_{A_s}/f_{B_s} = f^{AX}/f^{BX} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

This ratio, from definitions of f^{AX} and f^{BX}, is constant. Accordingly, one may transform eqn. (3) and write

$$K' = K(f_{B_s}/f_{A_s}) = B_z(1 - B_s)f_{B_z}/(B_s(1 - B_z)f_{A_z} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Following Kielland (*J. Soc. Chem. Ind.*, **1935**, **54**, 232T) one may give for either ion in the exchanger

$$\log f_{A_z} = CB_z^2; \ \log f_{B_z} = CA_z^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

FIG. 5. *Uni-univalent exchange isotherms of chabazite. Scales of ordinates and abscissæ give ion fractions in solutions and in crystals respectively, and subscripts " s " and " z " refer to these ions in solution and in the zeolite respectively.*

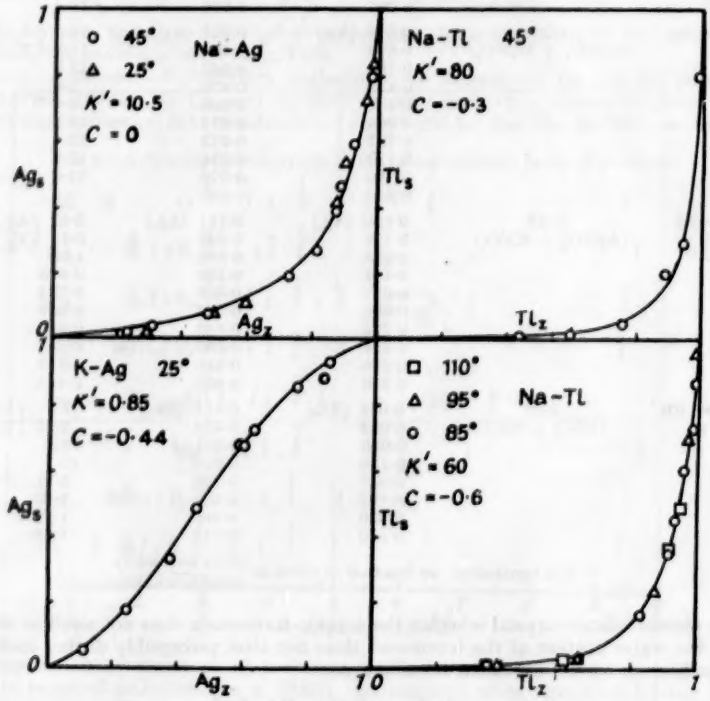


TABLE 7. Na ⟶ Tl *Exchanges at several temperatures using* $NaNO_3 + TlNO_3$ *at constant total normality of* 0·25.

Temp.	Equiv. ion fraction Tl in solution	Equiv. ion fraction Tl in zeolite	Mass action quotient $\frac{Tl_zNa_s}{Tl_sNa_z}$	Temp.	Equiv. ion fraction Tl in solution	Equiv. ion fraction Tl in zeolite	Mass action quotient $\frac{Tl_zNa_s}{Tl_sNa_z}$
110°	0·0096	0·356	57·0	85°	0·0068	0·361	78·8
	0·027	0·602	54·1		0·027	0·633	61·7
	0·360	0·918	19·9		0·161	0·830	25·5
	0·488	0·955	22·2		0·352	0·913	19·3
95	0·0064	0·394	81·4		0·452	0·928	15·6
	0·031	0·640	55·2		0·599	0·956	14·5
	0·235	0·876	23·0		0·726	0·986	26·6
	0·353	0·914	19·5		0·866	0·988	12·7
	0·699	0·975	16·8	45	0·0092	0·438	83·9
	0·960	0·995	8·21		0·016	0·598	89·3
					0·046	0·759	65·3
					0·203	0·887	30·8
					0·291	0·943	40·3
					0·798	0·984	15·6

Then provided the constant C is the same for each ion, eqn. (8) gives

$$\log f_{B_z}/f_{A_z} = C(A_z^2 - B_z^2) = C(B_z + A_z)(A_z - B_z) = C(1 - 2B_z) \quad . \quad . \quad (9)$$

because $B_z + A_z = 1$. Combination of eqns. (9) and (7) then gives eqn. (2).

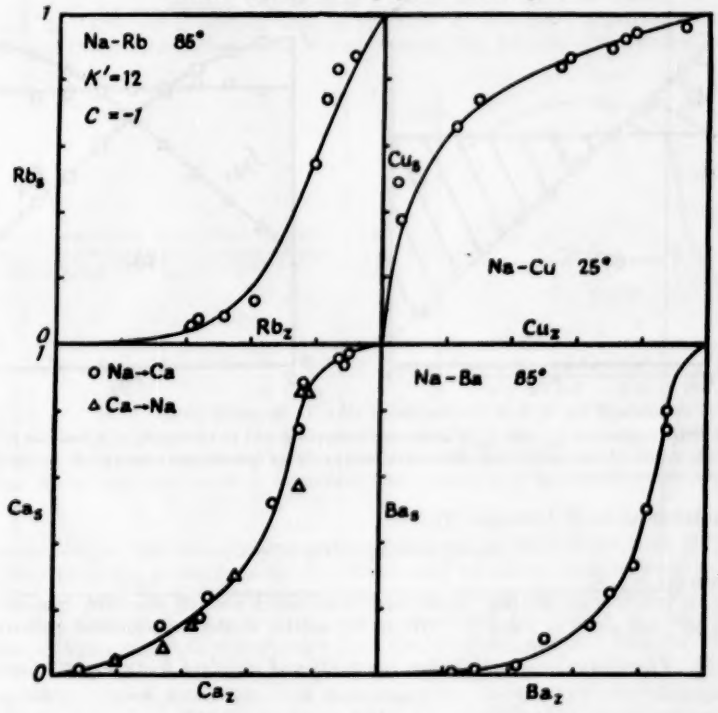
We may also obtain eqn. (2) by starting from the mass-action equilibrium constant in the form

$$B_z(1 - B_s)/B_s(1 - B_z) = K_0 \exp(-\Delta E/\boldsymbol{R}T) \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where K_0 is a constant and ΔE is the energy of exchange per g.-ion of B cations entering or of A cations leaving the crystal. If we now write

$$\Delta E = \Delta E_0(1 + aB_s) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

FIG. 6. *Uni-uni- and uni-bi-valent exchange isotherms of chabazite. The scales of ordinates and abscissæ have the same significance as in Fig. 5.*



where ΔE_0 and a are constants, then eqns. (10) and (11) combined give

$$\log \frac{B_z(1 - B_s)}{B_s(1 - B_z)} = \log \left(K_0 - \frac{\Delta E_0}{2{\cdot}30\boldsymbol{R}T} \right) - \frac{a\Delta E_0}{2{\cdot}30\boldsymbol{R}T} B_s \quad . \quad . \quad . \quad . \quad (2a)$$

which has the same form as eqn. (2).

The above procedure is empirical. However, in the not wholly dissimilar problem of adsorption with interaction, the first approximation leads to an isotherm with the additional linear term analogous to that in B_z in eqn. (2*a*) (Fowler and Guggenheim, "Statistical Thermodynamics," Cambridge Univ. Press, 1939, p. 429 *et seq.*). Investigation of ion-exchange models for crystals leading more rigorously to equations such as (2*a*) will be made elsewhere.

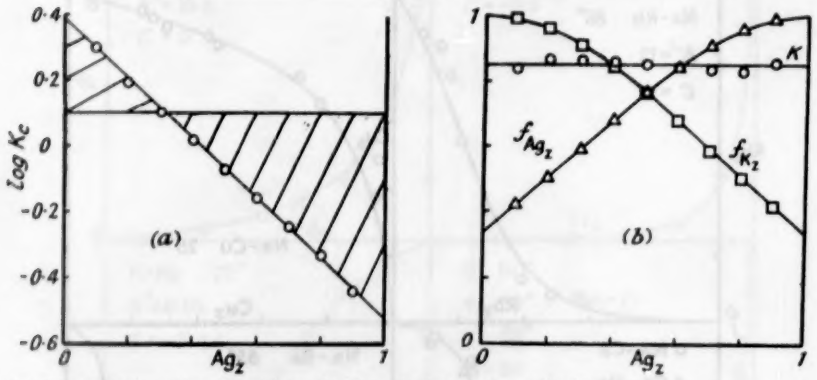
Calculation of f_{B_z}/f_{A_z} and of Thermodynamic Equilibrium Constants K.—The method of Ekedahl, Hogfeldt, and Sillen (*Acta Chem. Scand.*, 1950, **4**, 556) was used to calculate f_{B_z}/f_{A_z}. The quotients $K_c = [B_z(1 - B_s)/B_s(1 - B_z)](f_A/f_B)_s$ were calculated for a series of values of B_s.

$(f_A/f_B)_z = f^{AX}/f^{BX}$ (eqn. 6) was computed by using Conways' activity coefficients ("Electrochemical Data," Elsevier, 1952) and assuming for each electrolyte that this ratio was independent of temperature. A typical curve of log K_c against Ag_z is shown (for the K–Ag exchange) in Fig. 7*a*. Then at any value of Ag_z, $-\log f_{K_z}$ is the cross-hatched area to the right of the chosen value of Ag_z. The activity coefficients f_{K_z} and f_{Ag_z} as functions of Ag_z are shown in Fig. 7*b*. Moreover, from their ratios and from K_c, the true thermodynamic equilibrium constant, K, is derived. The self-consistency of the method is shown in Fig. 7*b*, where the values of K computed for various values of Ag_z are all the same.

Provided the plot of log K_c against B_z is linear, the thermodynamic equilibrium constant must be the value of K_c where $B_z = \frac{1}{2}$. This follows from eqn. (2), by substituting in it the expression $K_c(f_B/f_A)_z = B_z(1 - B_z)/B_z(1 - B_z)$. We now have on rearranging eqn. (2)

$$\log K_c = 2CB_z + \log K' - \log f_A/f_B - C \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

FIG. 7.



(a) *The variation of* log K_c *with ion fraction of silver in the zeolite* (Ag_z).

(b) *Activity coefficients* f_{Ag_z} *and* f_{K_z} *of silver and potassium ions in chabazite, as a function of* Ag_z. *The degree of constancy of the thermodynamic exchange equilibrium constant, K, is seen from the horizontal line.*

But, on substitution for K' from eqn. (7),

$$\log K_c = 2CB_z + \log K - C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

so that when $B_z = \frac{1}{2}$, $K_c = K$.

Values of the thermodynamic equilibrium coefficients and of standard free energies of exchange, ΔG°, are given in Table 8. Within the scatter of the experimental isotherm points

TABLE 8. *Thermodynamic equilibrium constants and standard free energies of exchange.*

Exchange pair	Temp.	Equil. const. K	ΔG° (cal./g.-ion)	ΔS° (e.u.)
Na ⟶ Ag	25—45°	11·4	−1440	+4·8 (25°)
Na ⟶ Rb	85	12·6	−1500	—
Na ⟶ K *	25	13·3	−1530	—
Na ⟶ Tl	45	96·2	−2900	—
Na ⟶ Tl	85—110	72·1	−3040 (85°)	+8·5 (85°)
K ⟶ Ag	25	0·855	+100	—

* Calculated equilibrium from Na–Ag and K–Ag exchange isotherms.

(cf. Fig. 5) the temperature coefficients of the exchange equilibrium are all notably small. There is no observable shift in this equilibrium for the sodium–silver exchange between 25° and 45°, or for the sodium–thallium exchange between 85° and 110°. The variation of K with temperature is $\partial \ln K/\partial T = -\Delta H^\circ/RT^2$, so that for the above exchanges $\Delta H^\circ \simeq 0$. Accordingly, one may compute $\Delta S^\circ \simeq -\Delta G^\circ/T$, as given in col. 5 of Table 8. There are few data with which to compare the thermodynamic results of Table 8, although Coleman (*Soil Sci.*, **1952**, **74**, 115), for the Na ⟶ K exchange in two Amberlite resins, gave ΔG° equal to +400 and +498 cal./g.-ion at 25°.

Uni-bivalent Exchange Equilibria.—Exchanges of the type $2A^+ \rightleftharpoons B^{2+}$ gave the isotherms in Fig. 6. The exchange $2Na^+ \longrightarrow Cu^{2+}$ is exceptional in that the bivalent ion shows a smaller affinity for chabazite than sodium and so is more concentrated in solution than in the crystals; with the bivalent ions Ca^{2+} and Ba^{2+} the converse is the case. The method of Hogfeldt, Ekedahl, and Sillen appropriately modified (*Acta Chem. Scand.*, 1950, **4**, 828) can in principle still be applied. For NaCl–$CaCl_2$ of total normality 0·5, such as comprised the equilibrium solutions in the sodium–calcium exchange of Fig. 6, the ratio $f_{Na_2}^2/f_{Ca_2}$ was calculated by using Glueckauf's equation and assuming as previously that this ratio did not depend on temperature. The variation in the ratio is large; and the corresponding plot of log K_c against the ion fraction, Ca_z, exhibits a maximum (Fig. 8). This complicates the graphical integrations required to derive f_{Na_2} and f_{Ca_2}, and thence to obtain the thermodynamic equilibrium constant. Since also there are no experimental data with which the calculated ratios $f_{Na_2}^2/f_{Ca_2}$ can be compared, the procedure was not carried further.

The curve of log K_c against Ca_z is of the same shape as that drawn by Hogfeldt (*ibid.*, 1951, **5**, 1400) for a system with a constant K showing "compound formation." The meaning of this term is rather vague, but may imply that for a certain composition the free

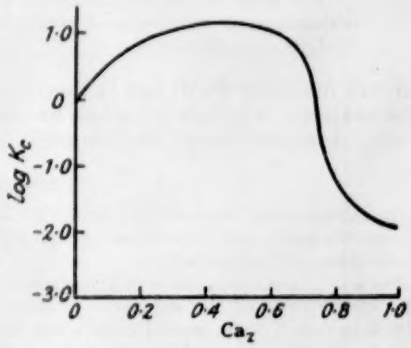


FIG. 8. *The maximum exhibited in the curve of K_c vs. the ion fraction of dissolved calcium for the exchange* $2Na^+ \rightleftharpoons Ca^{2+}$.

energy of the system has a minimum value. In the zeolite this could mean that a distribution of ions and water molecules with a minimum free energy is possible for a certain cationic composition.

Discussion.—The sodium–cæsium exchange, using N/4-(NaCl + CsCl) at 25°, has not been referred to in the previous sections. Practically all the exchanges went to between 60 and 75% Cs, and further treatments with more concentrated cæsium chloride gave little further interchange. Again it appears that about two-thirds of the sodium in Na-chabazite differs in ease of replacement from the last third, as noted with the $2Na^+ \rightleftharpoons Ca^{2+}$ reaction.

The reversibility of exchange was demonstrated directly by studying both the $2Na \longrightarrow Ca$ and the $Ca \longrightarrow 2Na$ reaction. It is also notable that no evidence of limited miscibility of any pair of cationic forms of chabazite appears and there are no intermediate horizontal sections in the isotherms such as were observed in $Na \rightleftharpoons K$ exchange in analcite (Barrer and Hinds, *loc. cit.*).

The heavier ions in general show a greater affinity for the crystals than do lighter ones. The affinity sequence from Table 8 is $Na < Ag < Rb < K < Tl$. There is little distinction between Ag, Rb, and K, however, and the high affinity of the higher ion, K, is anomalous.

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Kinetic Studies of the Oxidation of Aromatic Compounds by Potassium Permanganate. Part III. Ethylbenzene.*

By C. F. Cullis and J. W. Ladbury.

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A kinetic study of the oxidation of ethylbenzene and some related compounds is described. Initial attack of ethylbenzene occurs predominantly at the α-carbon atom to yield acetophenone as the first isolable product, which is slowly further oxidised to benzoic acid; measurements of carbon dioxide evolution suggest that there is little, if any, disruption of the aromatic ring.

Studies of the influence of added salts suggest that the Mn^{3+} ion, which is believed to be the principal oxidising entity in the oxidation of toluene, plays a less important rôle in the reactions of ethylbenzene and other compounds containing a β-carbon atom in the side-chain.

The form of the reaction–time curves exhibited by some oxygenated derivatives of ethylbenzene, and the influence of structure on ease of oxidation, are discussed.

Part I of this series (Cullis and Ladbury, *J.*, 1955, 555) described a kinetic investigation of the oxidation of toluene by potassium permanganate. This has now been extended to the next higher homologue, ethylbenzene.

Experimental

The experimental methods were similar to those described in Part I. The solvent was 54·2% w/v aqueous acetic acid. Solutions of 2-phenylethanol and phenylacetaldehyde were stored in an atmosphere of carbon dioxide.

Products of the Oxidation of Ethylbenzene.—Ether-extracts containing the neutral and the acidic constituents of the oxidation products were obtained by a method similar to that outlined in Part I. The neutral extract was dried (Na_2SO_4) and the ether was evaporated under reduced pressure. The residue was cooled to 5°, and the supernatant liquid decanted. Both phases were fractionally distilled. The solid contained a small amount of unchanged ethylbenzene (b. p. 136°; lit., 136°) but mainly acetophenone [b. p. 201° (lit., 202°); 2 : 4-dinitrophenylhydrazone, m. p. 249° (lit., 249°)]. The liquid decanted from the crystals was largely ethylbenzene, with smaller amounts of acetophenone. Tests with α-naphthyl *iso*cyanate showed that no appreciable quantity of 1-phenylethanol (lit., b. p. 205°) was present in the residues of the two distillates.

The ether from the acidic extract was evaporated, leaving colourless crystals soluble in hot, but insoluble in cold water. Recrystallisation from water yielded benzoic acid, m. p. and mixed m. p. 121° (lit., m. p. 121°). The mother-liquor was acidified and washed with ether. This extract was dried (Na_2SO_4); it gave no precipitate when 2 : 4-dinitrophenylhydrazine in aqueous alcohol was added, thus indicating the absence of ketonic acids. The ether extract and the mother-liquor gave negative tests for phenols with diazotised *p*-nitroaniline.

The only products found are thus acetophenone (about 50% yield), benzoic acid, and carbon dioxide. Thus oxidation probably occurs predominantly at the α-carbon atom (cf Cavill and Solomon, *J.*, 1954, 3943). The absence of β-oxygenated intermediates might be due to their being further rapidly oxidised as fast as they are formed. The observed rates of oxidation of β-oxygenated compounds (Table 3) show, however, that, if the β-carbon atom in ethylbenzene suffers appreciable oxidative attack, it should be possible to isolate 2-phenylethanol and phenylacetic acid. Yet they were not found.

Results and Discussion

Evolution of Carbon Dioxide.—The amount of carbon dioxide evolved during the oxidation of ethylbenzene corresponded to complete oxidation of 7·8% of the combined carbon in this molecule (Table 1). Oxidation to carbon dioxide of one carbon atom per

* Part II, *J.*, 1955, 1407.

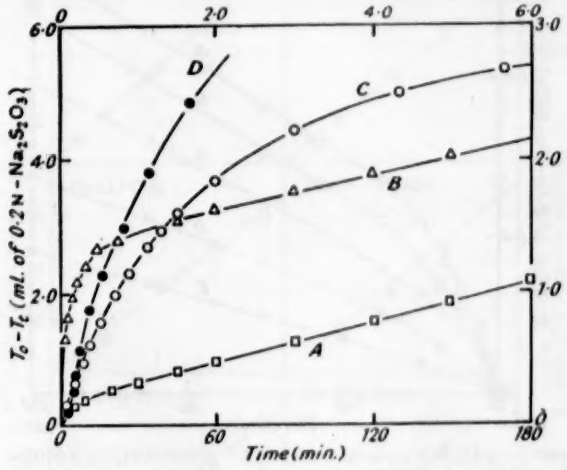
molecule, as would occur if ethylbenzene was oxidised completely to benzoic acid, would, on the other hand, correspond to a value of 12·5%. The difference is no doubt due to incomplete oxidation of acetophenone to benzoic acid.

TABLE 1.

Temp.: 50°. Solvent: 54·2% w/v aqueous acetic acid. [PhEt] = 0·0103M; [$KMnO_4$] = 0·103M.

PhEt taken (g.)	$BaCO_3$ (g.) (corrected for oxidn. of solvent)	CO_2 (g.)	PhEt completely oxidised (%)
0·106	0·1212	0·0270	7·7
0·106	0·1242	0·0276	7·9

FIG. 1. *Reaction–time curves for the oxidation of ethylbenzene and related compounds.*



Temp.: 50°. Solvent: 54·2% w/v aqueous acetic acid.

[Organic compound] = 0·0103M; [$KMnO_4$] = 0·0206M.

A, Acetophenone. *B*, Phenylacetaldehyde. *C*, Ethylbenzene. *D*, 2-Phenylethanol.

(The left-hand ordinates refer to ethylbenzene, 2-phenylethanol, and phenylacetaldehyde, and the right-hand ordinates to acetophenone. The lower abscissæ refer to ethylbenzene, acetophenone, and 2-phenylethanol, and the upper abscissæ to phenylacetaldehyde. The ordinate values may be converted into "moles of $KMnO_4$ per litre" by multiplication by the factor: $3·442 \times 10^{-3}$.)

The number of moles of carbon dioxide produced is approximately equal to the number of moles of benzoic acid formed at any stage. This suggests that the carbon dioxide evolved is derived from the β-carbon atom in ethylbenzene, and that ring fission occurs, if at all, only to a comparatively small extent.

The Development of Reaction with Time.—Reaction–time curves for the oxidation of ethylbenzene and some associated compounds are shown in Fig. 1. With ethylbenzene, as with toluene, autocatalysis is not observed. The reaction–time curves for 2-phenylethanol show slight sigmoid character. With acetophenone and phenylacetaldehyde, a high initial oxidation rate is found, which falls off rapidly to give an almost linear curve. When the permanganate concentration alone is varied, the linear portions of the curves are almost parallel (Fig. 2), suggesting that the oxidation eventually becomes controlled largely by the rate of some internal rearrangement, such as enolisation, of the molecule of the organic compound (cf. Lejeune, *Compt. rend.*, 1926, **182**, 694; Drummond and Waters, *J.*, 1953, 440; 1955, 497).

With acetophenone, the observed behaviour may be accounted for if, in the system :

$$Ph{\cdot}CO{\cdot}CH_3 \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} Ph{\cdot}C(OH){:}CH_2 \quad . \quad . \quad . \quad . \quad . \quad (1)$$

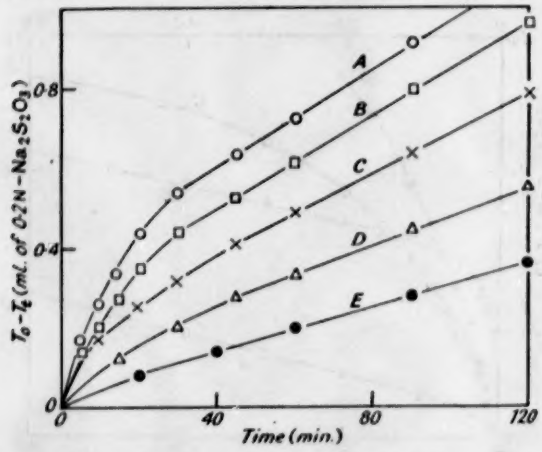
$$Ph{\cdot}CO{\cdot}CH_3 + KMnO_4 \xrightarrow{k_2} \text{Oxidation products} \quad . \quad . \quad . \quad . \quad (2)$$

$$Ph{\cdot}C(OH){:}CH_2 + KMnO_4 \xrightarrow{k_3} \text{Oxidation products} \quad . \quad . \quad . \quad . \quad (3)$$

it is assumed that $k_3 > k_1 > k_2$. In the early stages, the rate of oxidation will be given by :

$$k_2[Ph{\cdot}CO{\cdot}CH_3][KMnO_4] + k_3[Ph{\cdot}C(OH){:}CH_2][KMnO_4]$$

FIG. 2. *Reaction–time curves for the oxidation of acetophenone.*



Temp. : 50°. Solvent : 54·2% w/v aqueous acetic acid. $[Ph{\cdot}CO{\cdot}CH_3] = 0{\cdot}0103$M. $[KMnO_4]$ varied : *A*, 0·0410M ; *B*, 0·0311M ; *C*, 0·0206M ; *D*, 0·0103M ; *E*, 0·0052M.

As reaction proceeds, the concentration of the enol form will be reduced until (1) becomes rate-controlling with respect to (3). In these circumstances, the overall rate is equal to :

$$k_2[Ph{\cdot}CO{\cdot}CH_3][KMnO_4] + k_1[Ph{\cdot}CO{\cdot}CH_3]$$

and since $k_1 > k_2$, the rate of oxidation depends only to a small extent on the permanganate concentration, as shown by the slight divergency of the almost parallel reaction–time curves in Fig. 2.

If the rates of oxidation, following the initial rapid stage of reaction, are plotted against the permanganate concentration, extrapolation to zero concentration of oxidising agent should, according to the mechanism outlined, give a rate equal to $k_1[Ph{\cdot}CO{\cdot}CH_3]$, the rate of enolisation of the ketone. The extrapolated oxidation rate, calculated on the assumption that reaction takes place according to the equation

$$3Ph{\cdot}CO{\cdot}CH_3 + 8KMnO_4 + H_2O \longrightarrow 3Ph{\cdot}CO_2H + 3CO_2 + 8KOH + 8MnO_2$$

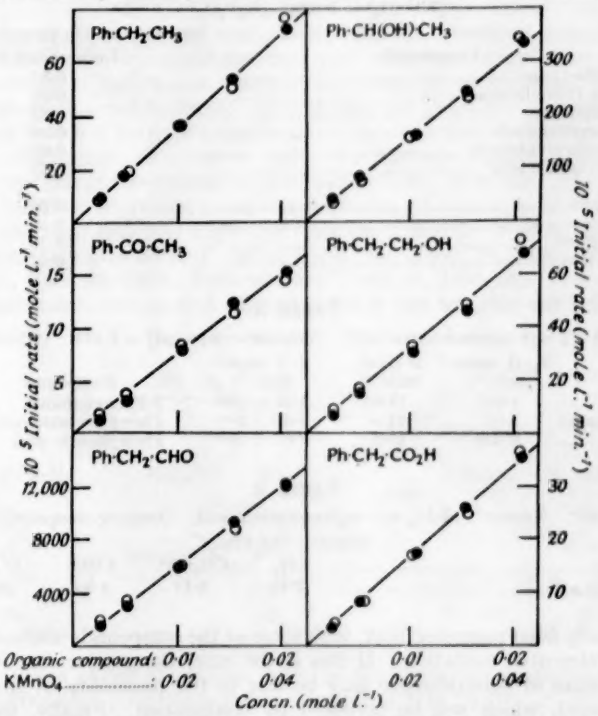
is found to have the value $1{\cdot}40 \times 10^{-6}$ mole of acetophenone $l.^{-1}$ $min.^{-1}$. The rate of enolisation of acetophenone, recently determined in this laboratory by Mr. M. H. Hashmi, by means of iodine uptake is $1{\cdot}22 \times 10^{-6}$ mole $l.^{-1}$ $min.^{-1}$ under conditions identical with those in the oxidation experiments. The satisfactory agreement between the two values supports the suggestion that enolisation is an important factor controlling the rate of oxidation of acetophenone.

Influence of Reactant Concentrations.—The reactions of potassium permanganate with

ethylbenzene and many associated compounds are initially of the first order with respect to each reactant. This can be seen from plots of initial rate against initial concentration of the two reactants when these are varied separately (Fig. 3). Second-order kinetics are, however, never maintained as reaction proceeds. The exhibition of comparatively simple behaviour initially, followed by a change to more complex kinetics, is frequently observed in studies of oxidation by potassium permanganate (Hinshelwood, *J.*, 1919, **115**, 1180; Musgrave and Moelwyn-Hughes, *Trans. Faraday Soc.*, 1933, **29**, 1162; Hinshelwood and Winkler, *J.*, 1936, 368).

Influence of Added Salts.—In presence of a large concentration of pyrophosphate ions,

FIG. 3. *The dependence of initial oxidation rate on reactant concentrations.*



Temp.: 50°. Solvent: 54·2% w/v aqueous acetic acid.
○ [Organic compound] = 0·01M; [$KMnO_4$] varied.
● [$KMnO_4$] = 0·02M; [Organic compound] varied.

which form a comparatively stable complex with Mn^{3+} ions (Merz, Stafford, and Waters, *J.*, 1951, 638), the rates of oxidation of ethylbenzene and related compounds are reduced to about 60% of their original values (Table 2). Comparison of these results with those obtained for some other aromatic compounds shows that the proportion of oxidation effected by manganic ions depends quite markedly on the nature of the substrate. It appears that, with compounds containing a β-carbon atom, the Mn^{3+} ion is a less important oxidising entity than with toluene and the xylenes.

Influence of Structure.—Table 3 gives the values of the second-order velocity constants for the initial reaction at 50°, together with the Arrhenius parameters, for the oxidation of ethylbenzene and some related compounds. The values of ethylbenzene and the β-oxygenated derivatives may be compared with those for toluene, benzyl alcohol, benzaldehyde, and benzoic acid (Table 4).

The greater rate of oxidation of ethylbenzene, as compared with toluene, may be attributed to the increased electron density on the α-carbon atom due to the presence of the adjacent methyl group. The fact that 2-phenylethanol is less readily oxidised than benzyl alcohol must be due to the fact that the inductive effect of the ring is diminished by the presence of an interposed methylene group, which prevents the enhancement of polarisation of the O–H bond. Thus the α-carbon atom in 2-phenylethanol does not suffer to the same extent as that in benzyl alcohol the increased electron density due to the electronegativity of the oxygen atom.

TABLE 2.

Temp.: 50°. Solvent: 54·2% w/v aqueous acetic acid. [Organic compound] = 0·01M; $[KMnO_4]$ = 0·02M; $[K_4P_2O_7]$ = 0·02M.

Compound	Inhibited rate in presence of $K_4P_2O_7$ / Uninhibited rate
Ethylbenzene	0·62
(±)-1-Phenylethanol	0·67
Acetophenone	0·61
2-Phenylethanol	0·50
Phenylacetaldehyde	0·68
Phenylacetic acid	0·65
Toluene	0·30
o-Xylene	0·50
m-Xylene	0·36
p-Xylene	0·47

TABLE 3.

Solvent: 54·2% w/v aqueous acetic acid. [Organic compound] = 0·01M; $[KMnO_4]$ = 0·02M.

Compound	k_{50} (l. mole^{-1} min.$^{-1}$)	E (kcal. mole^{-1})	A (l. mole^{-1} min.$^{-1}$)	Compound	k_{50} (l. mole^{-1} min.$^{-1}$)
Ethylbenzene	1·89	14·8	$1·87 \times 10^{10}$	2-Phenylethanol	1·65
(±)-1-Phenylethanol	8·04	14·8	$8·49 \times 10^{10}$	Phenylacetaldehyde	300
Acetophenone	0·355	15·9	$2·07 \times 10^{10}$	Phenylacetic acid	0·675

TABLE 4.

Temp.: 50°. Solvent: 54·2% w/v aqueous acetic acid. [Organic compound] = 0·01M; $[KMnO_4]$ = 0·02M.

R	CH_3	$CH_2{\cdot}OH$	CHO	CO_2H
$k_{Ph\cdot CH_2R}/k_{PhR}$	2·41	0·17	4·96	23·3

It has already been suggested that, with some of the compounds studied, the enol form may suffer preferential oxidation. If this is the case, the greater reactivity of phenylacetaldehyde than of benzaldehyde may be due to the possibility of enolisation in the former compound, which will be favoured by conjugation. Finally, the high rate of oxidation of phenylacetic acid, relative to that of benzoic acid, is in accord with the fact that side-chain carbon atoms are generally more susceptible to attack than carbon atoms in the aromatic ring, unless the latter positions are activated by the presence of substituents such as hydroxyl (Hinshelwood, *loc. cit.*) or methyl (Cullis and Ladbury, *loc. cit.*).

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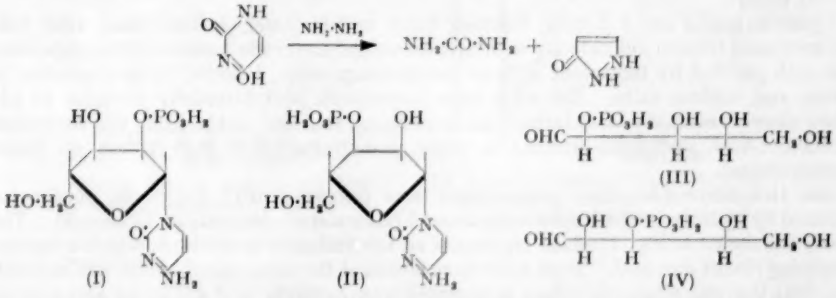
Nucleotides. Part XXXIII. The Structure of Cytidylic Acids* a *and* b.

By (Mlle.) F. Baron and D. M. Brown.

[Reprint Order No. 6263.]

Fission of cytidylic acid *a* and *b* by hydrazine yields ribose 2- and 3-phosphate respectively, characterised by, *inter alia*, comparison with the sugar phosphates derived from adenylic acid *a* and *b* by acid hydrolysis. Uridylic acid *b* yields the same ribose phosphate as does cytidylic acid *b*. The *a* and the *b* isomers of these nucleotides are therefore the 2′- and 3′-phosphates, respectively, of the ribonucleosides.

Fosse, Hieulle, and Bass (*Compt. rend.*, 1924, **178**, 811) described a reaction between hydrazine and uracil whereby pyrazolone and urea were formed and most conveniently isolated as xanthhydryl derivatives. Levene and Bass (*J. Biol. Chem.*, 1927, **71**, 167) later showed that uridine and hydrazine hydrate afforded pyrazolone and, they presumed, ribosylurea, their inability to isolate the latter being attributed to the high solubility of its xanthhydryl derivative. We saw in these observations a possible solution to the problem of the structure of the pyrimidine mononucleotides. Meanwhile, physical evidence has been given, based on ultraviolet and infrared spectra, p*K* values, and solution densities, supporting the view that cytidylic acid *a* and *b* are the 2′ and the 3′ phosphate of cytidine (I and II), respectively (Cavalieri, *J. Amer. Chem. Soc.*, 1952, **74**, 5804; Fox, Cavalieri, and Chang, *ibid.*, 1953, **75**, 4315; Michelson and Todd, *J.*, 1954, 34). The present work affords confirmation and was carried through since it was felt that rigid chemical proof was necessary.



For the orientation of the phosphoryl group in the monoribonucleotides derived from nucleic acids, degradative procedures generally applicable to the sugars are not feasible. Methylation leads to phosphoryl migration (Brown, Magrath, and Todd, *J.*, 1954, **1442**) and acylation leads to cyclic phosphates (*idem*, *J.*, 1952, 2708). Removal of the aglycone, effected by acid hydrolysis, is accompanied by phosphoryl migration (cf. Brown and Todd, *J.*, 1952, 44). Khym *et al.* (*J. Amer. Chem. Soc.*, 1953, **75**, 1262; 1954, **76**, 1818, 5523) showed that during the treatment of adenylic acids *a* and *b* with the sulphonic acid resin Dowex-50 in the hydrogen form, phosphate migration proceeds more rapidly that hydrolysis of the glycosidic linkage so that a mixture of ribose 2-phosphate (III) and ribose 3-phosphate (IV) is obtained from either the *a* or the *b* acid. The liberated ribose phosphates are not significantly isomerised by the acidic resin, so that by using short hydrolysis times they were able to relate each ribose phosphate to its parent nucleotide. This procedure is inapplicable to the pyrimidine nucleotides since the *N*-glycosidic linkage in these compounds is very stable to hydrolysis.

No migration of the phosphate residue occurs in the isomeric nucleotides in alkaline solutions, a property they share with other polyhydroxyalkyl dihydrogen phosphates

* Part XXXII, *J.*, 1955, 2632.

(Brown and Todd, *loc. cit.*). In addition glycosylureas are unstable, decomposing to urea and a sugar under very mild conditions (Schoorl, *Rec. Trav. chim.*, 1903, **22**, 35). It seemed, therefore, that if fission by hydrazine could be applied to the isomeric uridylic or cytidylic acids, the corresponding ribose phosphates should be readily obtained, uncontaminated by products resulting from migration.

As a preliminary, uridine and cytidine were treated with hydrazine. The former, as reported by Levene and Bass (*loc. cit.*), yielded pyrazolone, and cytidine gave apparently 3-aminopyrazole. In neither case was free ribose produced although a material giving sugar reactions was present. A probable explanation is that further condensation of hydrazine with the liberated sugar or sugar ureide had occurred. Treatment of the product with benzaldehyde yielded a material indistinguishable on chromatograms from ribose, although this sugar was not produced by treatment with mineral acid or nitrous acid.

Reaction of hydrazine with the nucleotides was first studied with the readily accessible mixtures of the *a* and *b* isomers of uridylic and cytidylic acids. The reaction of hydrazine on uridylic acid was readily followed spectrophotometrically at 260 mμ, as the pyrazolone formed showed little or no absorption at that wavelength. With hydrazine hydrate at 70° reaction was complete in 10 minutes, and with 15% aqueous hydrazine in one hour. Cytidylic acid was more resistant, reaction being complete only in 70 minutes when hydrazine hydrate was used. 3-Aminopyrazole was probably the heterocyclic product in the latter case.

From the reaction mixture from either uridylic acid or cytidylic acid a phosphorus-containing acid was isolated as the barium salt. The product was clearly not barium diribosylurea phosphate, although it contained nitrogen. Paper chromatography indicated that this product was a sugar phosphate containing nitrogenous impurities. In accord with this, purification by absorption on an anion-exchange resin reduced the nitrogen content to zero.

Cytidylic acid *a* and *b* (Loring, Bortner, Levy, and Hammel, *J. Biol. Chem.*, 1953, **196**, 807) were next treated individually with hydrazine, and the crude barium ribose phosphate from each purified by treatment with an ion-exchange resin, followed by precipitation of barium and lithium salts. The salts were hygroscopic and extremely unstable at pH values above neutrality, the latter fact explaining the low yields from the hydrazine reaction. Acid hydrolysis yielded a sugar, indistinguishable from ribose on paper chromatograms.

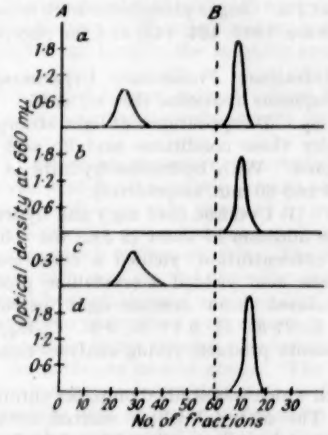
The two ribose phosphate preparations were compared with the ribose phosphates produced by hydrolysis of adenylic acids *a* and *b* (Khym *et al.*, *locc. cit.*) on Dowex-50. The results are shown in Fig. 1, which represents an ion-exchange analysis, in which a borate-containing eluant was used. Both acids were eluted at the same rate if borate was omitted. It is clear that one ribose phosphate is produced from cytidylic acid *a* (Fig. 1*c*) and another from cytidylic acid *b* (Fig. 1*b*). No cross contamination was observed, in accord with expectation. Uridylic acid *b* gave a sugar phosphate showing only one peak on the elution diagram (Fig. 1*d*) corresponding to that from cytidylic acid *b*. This confirms earlier work which showed that the phosphate residue occupies the same (although undefined) position in the ribofuranose residue of both nucleotides (Brown, Dekker, and Todd, *J.*, 1952, 2715). Khym *et al.* (*locc. cit.*), on the basis of ion-exchange characteristics and acceptable structural studies, show that the first eluted acid (Fig. 1*a*) is ribose 2-phosphate (III) while the second is ribose 3-phosphate (IV) (elution retarded owing to formation of an anionic 1 : 2-borate complex; cf. Khym and Cohn, *J. Amer. Chem. Soc.*, 1953, **75**, 1153). We have also reached the same conclusion. Paper chromatography in borate solutions afforded corroboration of the ion-exchange experiments. More important however was the action of alkali on the two ribose phosphates, illustrated in Fig. 2. Khym, Doherty, and Cohn (*J. Amer. Chem. Soc.*, 1954, **76**, 1818, 5523) also find that ribose 3-phosphate is degraded more rapidly than the 2-isomer. This order of instability is to be expected since the 3-phosphate should undergo β-elimination, a course not directly open to the 2-phosphate. Although this explanation differs from that of Khym, Doherty, and Cohn (*loc. cit.*), an easy base-catalysed elimination is shown by phosphate esters of other β-hydroxycarbonyl compounds which have been discussed earlier (Brown, Fried, and Todd, *Chem. and Ind.*, 1953, 352; *J.*, 1955,

2206). We are seeking confirmation of this view by a study of the products of alkaline fission of these and other sugar phosphates.

When treated with acid the sugar phosphates yielded ribose, the isomer considered to be ribose 2-phosphate (from cytidylic acid *a*) reacting faster than the other isomer. This is the order of hydrolysis rates found for the analogous glucose phosphates (Farrar, *J.*, 1949, 3131).

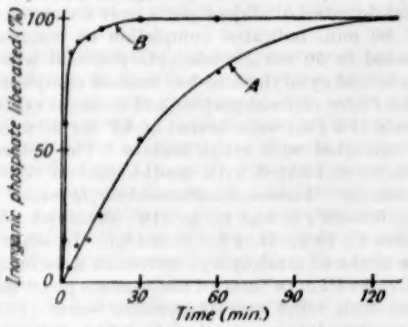
The above evidence points to the fact that cytidylic acid *a* yields ribose 2-phosphate, and cytidylic acid *b* yields ribose 3-phosphate. Cytidylic acids *a* and *b* are therefore cytidine-2′ and -3′ phosphate respectively. This conclusion can be reached independently, if it be accepted that the kinetic study by Khym *et al.* (*J. Amer. Chem. Soc.*, 1954, **76**, 1818) truly relates the first eluted acid (Fig. 1*a*) to adenylic acid *a* and the second to adenylic acid *b*. From the present study cytidylic acids *a* and *b* stand in the same relation to the

FIG. 1. *Ion-exchange analysis of ribose phosphates.*



a, Ribose 2- and 3-phosphate from adenylic acids *a* and *b*. *b*, *c*, and *d*, Ribose phosphates from cytidylic acid *b* and *a* and uridylic acid *b* respectively.

FIG. 2. *Rate of liberation of inorganic phosphate from the ribose phosphates by 0·2N-sodium hydroxide at 100°.*



A, Ribose phosphate from cytidylic acid *a* (ribose 2-phosphate). *B*, Ribose phosphate from cytidylic acid *b* (ribose 3-phosphate).

derived phosphates so that the phosphate group in, for example, cytidylic acid *a* must occupy the same relative position in the ribofuranose residue as that in adenylic acid *a*. Since three independent methods (Cavalieri, *loc. cit.*; Brown, Fasman, Magrath, Todd, Cochran, and Woolfson, *Nature*, 1953, **172**, 1184; Brown, Fasman, Magrath, and Todd, *J.*, 1954, 1448), in addition to that of Cohn and his co-workers, show unambiguously that adenylic acids *a* and *b* are adenosine-2′ and -3′ phosphate, it follows that cytidylic and uridylic acids *a* and *b* are the -2′ and -3′ phosphate of cytidine and uridine respectively. Further confirmation is being sought in collaboration with Dr. S. Varadarajan, by unambiguous synthesis in the uridylic acid series.

The bearing of these results on the orientation of the internucleotidic linkage in ribonucleic acids is apparent from earlier studies (*inter al.*, Brown and Todd, *J.*, 1953, 2040; Brown, Heppel, and Hilmoe, *J.*, 1954, 40; Whitfeld, *Biochem. J.*, 1954, **58**, 390).

EXPERIMENTAL

Cytidylic Acids a *and* b.—These were prepared by fractionation of yeast cytidylic acid according to Loring *et al.* (*loc. cit.*). The *a* isomer had $[\alpha]_D^{19}$ −4°, and the *b* isomer +47°, measured as the sodium salts at pH 7. Loring *et al.* give $[\alpha]_D^{24.5}$ −8° and +46°, respectively, for

the disodium salts. The purity of the two acids was confirmed by ion-exchange chromatography on Dowex-2 resin in the formate cycle (cf. Brown, Dekker, and Todd, *loc. cit.*).

Uridylic Acid b.—The crystalline sample was kindly supplied by Dr. D. I. Magrath (cf. Brown, Magrath, and Todd, *J.*, 1954, 1442). Its purity was confirmed by ion-exchange chromatography.

Ribose 2- and 3-Phosphate from Adenylic Acid a.—Adenylic acid *a* was hydrolysed in aqueous solution with Dowex-50 at 100° for 1 min. After filtration the solution was neutralised with barium hydroxide, and the mixed barium salts of ribose 2- and 3-phosphate were precipitated by addition of ethanol (cf. Khym and Cohn, *loc. cit.*). This preparation served as a standard for comparison with the ribose phosphates obtained by hydrazinolysis, including ion-exchange and paper-chromatographic methods.

Paper Chromatography.—When the solvent system propan-2-ol–1% aqueous ammonium sulphate (2 : 1) was used, ribose 2-, 3-, and 5-phosphate had almost identical R_P values (*ca.* 0·34). Later it was found that use of propan-2-ol–1% aqueous boric acid–10% ammonia (50 : 25 : 1) permitted the separation of the sugar phosphates with R_P values increasing in the order ribose 5-, 3-, 2-phosphate (*e.g.*, 0·05, 0·10, and 0·18 respectively). The R_P values were variable but the ratios R_P of 2-phosphate/R_P of 3-phosphate lay close about 1·5. Sugar phosphates were detected both with the aniline hydrogen phthalate (Partridge, *Nature*, 1949, **164**, 443) and the phosphate spray reagent (Hanes and Isherwood, *ibid.*, p. 1107).

Fission of Uridine and Cytidine Derivatives by Hydrazine; Preliminary Experiments.—(a) *Spectroscopic.* Uridine (10 mg.) was heated in 15% aqueous hydrazine (10 c.c.) at 65°. The optical densities of aliquot parts were measured at 260 mμ. Disappearance of light absorption after 80 min. indicated completion of reaction. Under these conditions uridylic acid was degraded in 50 min., while cytidylic acid was unaffected. With hydrazine hydrate at 65°, uridylic and cytidylic acid had reacted completely in 10 and 60 min. respectively.

(b) *Paper chromatographic and isolation experiments.* (1) Cytidine (540 mg.) and hydrazine hydrate (1·5 c.c.) were heated at 65° for 90 min. After addition of water (2 c.c.) the solution was extracted with ethyl acetate. The extract, on concentration, yielded a colourless oil which when treated with xanthhydrol in aqueous acetic acid yielded a crystalline product, presumably *3-amino-xx-dixanthhydrylpyrazole.* Crystallised from acetone–light petroleum (b. p. 60—80°) it had m. p. 216° (decomp.) (Found : C, 77·5; H, 5·4; N, 9·3. $C_{29}H_{21}O_2N_3$ requires C, 78·4; H, 4·8; N, 9·4%). In other experiments products giving analyses closer to those of the trixanthhydryl derivative were obtained.

Evaporation *in vacuo* of the aqueous phase gave an oil which was studied on paper chromatograms with ethyl acetate–pyridine–water (2 : 1 : 2). The material which reacted with the aniline phthalate reagent had R_P 0·38 but did not correspond to ribose (R_P 0·46). 0·1N-Hydrochloric acid at 100° did not affect the substance, but heating its aqueous solution with benzaldehyde, and then ether-extraction, gave a product in the aqueous phase corresponding on chromatograms to ribose. Similar chromatographic observations were made on the product derived from uridine.

(2) Uridylic acid *b* (1 g.) was heated at 65° for 90 min. with 15% aqueous hydrazine (15 c.c.). After concentration *in vacuo* the dried residual gum was dissolved in water and neutralised with barium hydroxide solution, and the barium salt precipitated by addition of ethanol (4 vol.). After reprecipitation the barium salt was dried at 50° *in vacuo* (Found : C, 18·3; H, 3·6; N, 7·5%). Other samples had various nitrogen contents. This material was studied further together with the corresponding product from cytidylic acid (see below).

The aqueous-ethanol filtrate from the barium salt was reduced to small bulk, and acetic acid added, followed by methanolic xanthhydrol. Next morning the solid product was collected, and washed with ethanol and then with hot water. Extraction with hot acetone, and concentration of the extract, gave dixanthhydrylpyrazolone, m. p. 215—217° (Found, in material dried at 80° *in vacuo* : C, 78·2; H, 4·7; N, 6·4. Calc. for $C_{29}H_{20}O_2N_2$: C, 78·3; H, 4·5; N, 6·3%). Dixanthhydrylpyrazolone was also obtained in corresponding reactions with uridine and 3-methyluracil. The material insoluble in acetone had m. p. 265—266° alone and in admixture with dixanthhydrylurea.

Cytidylic acid and hydrazine hydrate at 65° (90 min.) gave, after working up as in the case of uridylic acid, a barium salt (Found : C, 14·6; H, 3·1; N, 5·0%). This salt together with that derived from uridylic acid were studied on paper chromatograms with propan-2-ol–aqueous ammonium sulphate. The spots, detected with the aniline hydrogen phthalate or the phosphate reagent, corresponded in position to ribose 2-, 3-, or 5-phosphate.

In attempts to remove nitrogenous material from the barium salts they were treated in

aqueous solution with various reagents and then reprecipitated. Nitrogen content (N, 4%) was little reduced by nitrous acid or by overnight shaking at room temperature with benzaldehyde in di*iso*propyl ether (N, 3%) or with benzaldehyde at 100° for 15 min. (N, 4·6%). Treatment with Dowex-50 (H form) at 100° for 1 min. reduced the nitrogen content to *ca.* 1%. All of these treatments yielded salts showing only one sugar phosphate spot on paper chromatograms corresponding in its R_p value to ribose phosphate.

Anion-exchange Analyses of Ribose Phosphates.—For the ion-exchange analysis of the ribose phosphates from the hydrazinolysis a column (1 × 10 cm.) of the anion-exchange resin Dowex-2 (200—400 mesh) in the chloride form was employed, fractions (15 c.c.) being collected in an automatic fraction collector. Pentose was estimated in each fraction by Mejbaum's method (Brown, *Arch. Biochem.*, **1946**, **11**, 269) whereby 1 c.c. of solution and 3 c.c. of reagent were heated together at 100° for 20 min. and the optical density of the solution determined at 660 mμ (Fig. 1).

For elution of the ribose phosphates from the column, solvents closely similar to those used by Khym and Cohn (*locc. cit.*) were employed. Ribose 2-phosphate was eluted by a solution (*A*) containing ammonium chloride (0·05N), borax (0·01M), and ammonia (0·005M), which was followed by 0·05M-ammonium chloride (*B*) to elute ribose 3-phosphate. In other experiments the solvents, 0·0015M-sodium sulphate containing 0·0015M-borax, followed by 0·005M-sodium sulphate, were used, with the resin in the sulphate form. The results were similar to those with the chloride cycle.

The mixed barium salts of ribose 2- and 3-phosphate prepared from adenylic acid were used to standardise the column with respect to the position of elution of the ribose phosphates (Fig. 1*a*).

The following procedure was typical of that used with the cytidylic and uridylic acids. Cytidylic acid *b* (50 mg.) was heated with hydrazine hydrate (0·5 c.c.) at 70° for 60 min. and excess of hydrazine then removed by evaporation in a vacuum-desiccator. The residual gum was treated with saturated aqueous barium hydroxide (2·5 c.c.), and the solution immediately neutralised with carbon dioxide. The filtered solution was evaporated to dryness, redissolved in water with shaking, and after filtration treated with ethanol (4 vol.). The precipitated crude barium ribose phosphate was dissolved in water, stirred with Dowex-50, and filtered, and the solution then neutralised with ammonia to pH 8. After dilution to 25 c.c. the solution was put on the ion-exchange column, the column washed with water, and elution analysis carried out with the solutions named above. The elution diagram is shown in Fig. 1*b*. The only peak observed corresponded to that of ribose 3-phosphate.

Cytidylic acid *a* treated in the same way gave the elution diagram shown in Fig. 1*c*. The single peak corresponded to that of ribose 2-phosphate.

Uridylic acid *b* yielded a ribose phosphate corresponding to ribose 3-phosphate (Fig. 1*d*).

When mixtures of cytidylic acid *a* and *b* or uridylic acid *a* and *b* were employed, two peaks were always observed corresponding to ribose 2- and 3-phosphate.

In each case the fractions under the peak were pooled and percolated through a small Dowex-2 column (chloride form; 1 × 2 cm.), and the columns were eluted with 0·1N-hydrochloric acid. The effluent was neutralised with lithium hydroxide solution and concentrated *in vacuo*, and the product precipitated by ethanol. When run on chromatograms one spot was observed, corresponding to that of the ribose phosphate marker.

Ribose 2-Phosphate from Cytidylic Acid a.—The ammonium salt of cytidylic acid *a* (0·75 g.) and hydrazine hydrate (5 c.c.) were heated together at 65° for 60 min. After cooling, saturated barium hydroxide solution (10 c.c.) was added followed by acetone (200 c.c.), and the solution was kept overnight at 0°. The solid product was collected by centrifugation, washed with acetone, and dried. This barium salt was dissolved in water, barium removed by treatment with Dowex-50 resin (acid form), and the solution brought to pH 7·5 with dilute aqueous ammonia. After dilution to 300 c.c. the solution was percolated through a column of Dowex-2 (1 × 5 cm.; sulphate form). A ribose determination showed that 82% of the total reducing sugar had been retained on the column. Elution with 0·05M-sodium sulphate removed most of the product in the first 75 c.c. of eluate. This solution was treated with Dowex-50 to remove sodium ions, and then neutralised with aqueous barium hydroxide. Barium sulphate was centrifuged off, the solution concentrated under reduced pressure at 30°, and the barium ribose 2-phosphate precipitated by acetone. Part of this salt was further purified by reprecipitation twice from water, by ethanol (4 vol.). The hygroscopic material was dried *in vacuo* at 50° over phosphoric oxide (Found: C, 15·9; H, 4·4; P, 8·4. Calc. for $C_5H_9O_8PBa,H_2O$: C, 15·7; H, 2·9; P, 8·1%).

Another part of the crude barium salt was dissolved in water, the solution was clarified by

centrifugation, barium ions were removed by Dowex-50, and the lithium salt was prepared by adjustment to pH 7·0 with lithium hydroxide solution. The solution was concentrated *in vacuo* and *lithium ribose 2-phosphate* precipitated by addition of ethanol (4 vol.) in the cold. The very hygroscopic salt was centrifuged, washed with ethanol and ether and dried *in vacuo* at 30° (Found: C, 23·4; H, 4·6; P, 12·0. $C_5H_9O_8PLi_2,H_2O$ requires C, 23·1; H, 4·3; P, 11·9%).

Ribose 3-Phosphate from Cytidylic Acid b.—The above experiment was repeated with cytidylic acid *b*. The lithium salt was isolated and dried at 30° *in vacuo*. It was very unstable and hygroscopic, and still contained traces of lithium phosphate [Found: C, 22·6; H, 3·85; P(total), 12·5; P(organic), 11·3. Corrected for lithium phosphate: C, 23·7; H, 4·0; P, 11·9. Calc. for $C_5H_9O_8PLi_2,0·5H_2O$: C, 23·9; H, 4·0; P, 12·2%].

Ribose 2- and 3-phosphate, as their lithium salts, ran as single spots on chromatograms and had *R*, 0·34 and 0·21 respectively in propan-2-ol–1% aqueous ammonium borate (2 : 1).

Hydrolysis of Ribose 2- and 3-Phosphate.—(a) *Acid.* The substances, as their lithium salts, were heated in 0·1N-hydrochloric acid at 100°. Aliquot parts were analysed at intervals for inorganic phosphate. After 15, 30, and 60 min. respectively ribose 2-phosphate released 22, 35, and 56%, and ribose 3-phosphate 11, 21, and 50% of inorganic phosphate.

Paper chromatograms with butanol–acetic acid–water and ethyl acetate–pyridine–water disclosed ribose as the only sugar produced after complete hydrolysis.

(b) *Alkali.* The two acids, as their lithium salts, were heated in 0·2N-sodium hydroxide at 100°. Aliquot parts were analysed at intervals for liberated phosphate. The results are recorded in Fig. 2.

Our thanks are offered to Sir Alexander Todd, F.R.S., for stimulating discussions, to the Medical Research Council and the Centre Nationale de la Recherche Scientifique for an Exchange Fellowship (to F. B.), and to Dr. W. E. Cohn for helpful personal communications.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 24th,* 1955.]

2-*Acyl Derivatives of Cyclic* 1 : 3-*Diones. Part II.* The Structures of Angustione and Dehydroangustione.*

By W. R. CHAN and C. H. HASSALL.

[Reprint Order No. 6320.]

Angustione has been identified by synthesis as 2-acetyl-4 : 4 : 6-trimethyl-*cyclo*hexane-1 : 3-dione. Further evidence for the structure of dehydroangustione has been obtained by ozonolysis.

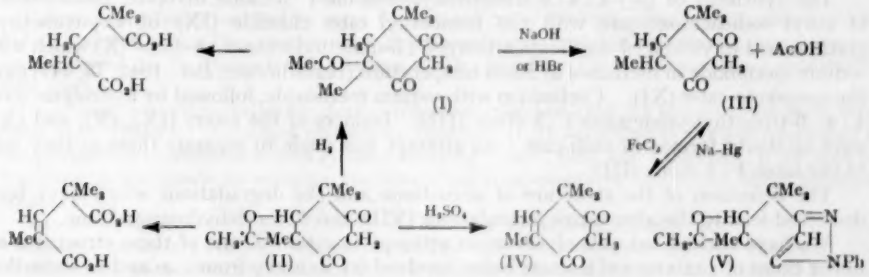
THE ketones angustione and dehydroangustione which occur in the essential oil of *Backhousia angustifolia* have been assigned the structures (I) and (II) respectively (Gibson, Penfold, and Simonsen, *J.*, 1930, 1184; Cahn, Gibson, Penfold, and Simonsen, *J.*, 1931, 286). Although these structures are based on extensive degradative studies there is no decisive evidence supporting them. In view of their unusual features we have sought unequivocal evidence.

The following properties have a particular bearing on the structural problem. Both angustione, $C_{11}H_{16}O_3$, and dehydroangustione, $C_{11}H_{14}O_3$, form copper chelate complexes, give anhydro-derivatives with hydroxylamine, substituted hydrazines, and ammonia, and condense with piperonaldehyde. Alkaline hydrolysis of angustione leads to a good yield of a compound $C_9H_{14}O_2$, formulated as 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (III) on the basis of oxidation experiments. Dehydroangustione is less susceptible to alkali but is hydrolysed by sulphuric acid to acetic acid and a β-diketone, $C_9H_{12}O_2$. As this diketone may be prepared from the diketone $C_9H_{14}O_2$ by oxidation with ferric chloride and gives αα*γ*-trimethylglutaconic acid on oxidation with sodium hypobromite, it is formulated as 4 : 6 : 6-trimethyl*cyclo*hex-4-ene-1 : 3-dione (IV). Dehydroangustione is converted quantitatively into angustione by catalytic hydrogenation.

Although structures (I) and (II) may be used to interpret the majority of the reactions

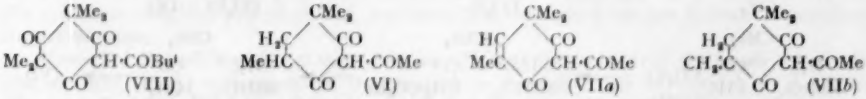
* The paper, *J.*, 1948, 50, is regarded as Part I.

of angustione and dehydroangustione they are not entirely applicable. The compound as (II) should not give a chloroform-soluble copper derivative or a ferric chloride colour in absolute alcohol. Such *cyclo*hexane-1 : 3-diones are "*trans*-fixed" (Eistert and Riess, *Chem. Ber.*, 1954, **87**, 92, 109; Henecka, "Chemie der β-Dicarbonylverbindungen," Springer-Verlag, Berlin, 1950, p. 279) and unable to form chelate complexes. We have confirmed that the related compound 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (III) gives no chelate derivatives with iron and copper salts. The structure (I) for angustione is not excluded in this way as there is the possibility of complex formation involving the enolised *cyclo*hexane-1 : 3-dione system and the acetyl grouping.



Also, the compound represented by (II) would not give anhydro-derivatives with hydroxylamine and substituted hydrazines. By Bredt's rule, such a bridged structure as (V) is excluded. In fact, the related compound dimedone gives normal mono- and di-oximes and hydrazones (Vorlander, *Annalen*, 1897, **294**, 253).

If angustione and dehydroangustione are assigned the structures (VI) and (VII*a* or *b*) respectively, there is no difficulty in accounting for all their properties. The formation of metal chelate complexes and anhydro-hydrazones has been observed (Briggs, Hassall, and Short, *J.*, 1945, 706) for the closely related compound leptospermone (VIII). The hydrolysis and oxidation reactions are readily explained in terms of the new structures. Structures (VI) and (VII*b*) have been suggested independently by Birch (*J.*, 1951, 3026), who pointed out that the nature of the condensation products formed with piperonaldehyde favoured the new structures.



Evidence in support of structure (VI) for angustione has been obtained from the consideration of ultraviolet absorption spectra and by synthesis. Simple *cyclo*hexane-1 : 3-diones, in ethanol, regularly give a single strong absorption peak at approximately 255 mμ. 2-Acyl*cyclo*hexane-1 : 3-diones under these conditions are characterised by two maxima, in the region of 230 and 275 mμ. The results in the Table indicate that angustione behaves

	$\lambda_{max.}$ (mμ)	ε	Ref.
4-Methyl*cyclo*hexane-1 : 3-dione	255	12,600	1
5 : 5-Dimethyl*cyclo*hexane-1 : 3-dione	258	12,000	2
4 : 4 : 6-Trimethyl*cyclo*hexane-1 : 3-dione	255	13,200	
4 : 4 : 6 : 6-Tetramethyl-2-*iso*valeryl*cyclo*hexane-1 : 3-dione *	234	8,920	
	281	10,800	
2-Acetyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione	231	10,000	3
	277	10,000	
2-Acetyl*cyclo*hexane-1 : 3-dione	235	14,700	4
	275	11,600	
Angustione	233	13,500	
	276	13,500	

* In *cyclo*hexane; the others in ethanol.

Refs.: 1, Meek, Turnbull, and Wilson, *J.*, 1953, 812. 2, Woodward and Blout, *J. Amer. Chem. Soc.*, 1943, **65**, 562. 3, Birch, *loc. cit.* 4, Smith, *J.*, 1953, 803.

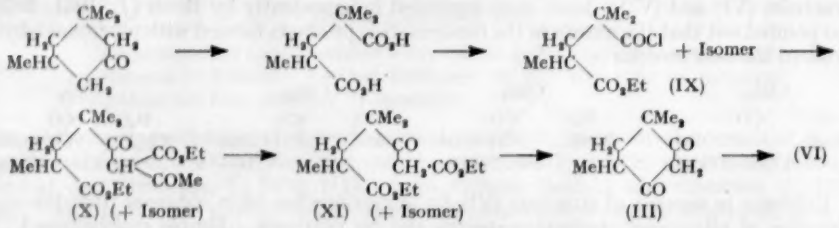
as a typical 2-acyl*cyclo*hexane-1 : 3-dione. The similarity of the ultraviolet absorption spectra of the amino-derivatives of angustione [$\lambda_{max.}$ 253, 290 mμ (ε 14,500, 14,500)] and of 2-acetyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione [$\lambda_{max.}$ 252, 288 mμ (ε 15,850, 15,850)] provides further evidence of the presence of the 2-acyl-1 : 3-dione structure in angustione.

(±)-4 : 4 : 6-Trimethyl*cyclo*hexane-1 : 3-dione (III) has been prepared by an unambiguous route and found to be identical with the product obtained from angustione on alkaline hydrolysis. When the dione is acetylated under conditions which have been applied for the introduction of a 2-acetyl group into related *cyclo*hexane-1 : 3-dione derivatives (Dieckmann and Stein, *Ber.*, 1904, **37**, 3380), (±)-angustione is formed.

The synthesis of (±)-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione involved condensation of ethyl sodioacetoacetate with the monoethyl ester chloride (IX) of ααγ-trimethylglutaric acid to yield 3 : 7-diethoxycarbonyl-5 : 5-dimethyloctan-2 : 4-dione (X) which with sodium methoxide in methanol at room temperature (Hunsdiecker, *Ber.*, 1942, **75**, 447) gave the monoketo-ester (XI). Cyclisation with sodium methoxide, followed by hydrolysis, gave 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (III). Isomers of the esters (IX), (X), and (XI) were no doubt formed in each case: no attempt was made to separate them as they lead to the same 1 : 3-dione (III).

The definition of the structure of angustione and the degradations which have been described lead to the alternative formulations (VII*a* and *b*) for dehydroangustione.

We have carried out ozonolyses in an attempt to establish one of these structures or, in the event of a mixture of isomers being involved (cf. α- and γ-irone; α- and β-citronellol; α- and β-geraniol; etc.), to obtain an indication of the proportion of (VII*b*) in the mixture. From dehydroangustione and aminodehydroangustione the maximum yield of formaldehyde was 6%. Although this result makes it very unlikely that a high concentration of (VII*b*) is present it cannot be used as an accurate measure of the proportion in dehydroangustione. There are various examples of low yields of formaldehyde from the ozonolysis of compounds containing $CH_2{:}CRR'$ groupings (Ruzicka, Seidel, Schinz, and Tavel, *Helv. Chim. Acta.*, 1948, **31**, 257). Also, there are cases where formaldehyde has been obtained from compounds which do not contain this group (Clemo and McDonald, *J.*, 1935, 1295; Karrer and Kebrle, *Helv. Chim. Acta*, 1952, **35**, 862).



Birch (*loc. cit.*) favours the structure (VII*b*) in view of the presence, in the infrared absorption spectrum of dehydroangustione, of peaks at 11·3 μ (888 cm.$^{-1}$) * and 6·1 μ (1640 cm.$^{-1}$). However, the fact that saturated hydrocarbons such as 3-ethylhexane show marked absorption near 890 cm.$^{-1}$ and both *cis*- and *trans*-3-methylpent-2-ene exhibit absorption between 1620 and 1660 cm.$^{-1}$ (Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915) confirms the assumption that compounds which do not contain $CH_2{:}CRR'$ groupings may give bands in these regions. Moreover, it is not certain that with such compounds as (VII*b*) the hydrogen out-of-plane deformations of the $CH_2{:}CRR'$ group should give rise to an absorption band at 890 cm.$^{-1}$. Although the frequency of this band normally lies between narrow limits (Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 44), it has been shown for aliphatic compounds that it may be shifted to 930 cm.$^{-1}$ through conjugation with a carbonyl group (Davison and Bates,

* Birch refers in his argument to a band at 11·75 μ but in the experimental section to a band at 11·3 μ. We have confirmed the presence of a band at 11·3 μ (888 cm.$^{-1}$), but not at 11·75 μ, and assume that the reference to the latter was a typographical error.

J., 1953, 2607). The intensity of absorption of the band at 890 cm.$^{-1}$ (38%) and others in this region is significantly less than that of bands at 1430—1500 cm.$^{-1}$ (69%) in the spectrum of dehydroangustione. If dehydroangustione existed only in the form (VII*b*) and the absorption at 890 cm.$^{-1}$ is ascribed to the $>C{=}CH_2$ group, a high intensity comparable to that at 1430—1500 cm.$^{-1}$ would be expected for this band (Werner and Sutherland, *J. Amer. Chem. Soc.*, 1952, **74**, 2689; Barnard *et al.*, *loc. cit.*)

The evidence does not permit a final decision on the composition of dehydroangustione but it does indicate that, if any of the isomer (VII*b*) is present, the proportion is small.

Experimental

Ultraviolet absorption spectra were determined on a Beckman spectrophotometer, model D.U. Infrared absorption spectra were determined on a Perkin-Elmer double-beam spectrometer (model 21 B), through the courtesy of Dr. Seymour Bernstein, Lederle Laboratories, New York.

αγγ- and αaγ-Trimethyladipic Acid.—Dihydro*iso*phorone (250 g.) was oxidised with 50% nitric acid (1320 c.c.) containing ammonium vanadate (1 g.), according to the procedure used in the preparation of adipic acid from *cyclo*hexanol (*Org. Synth.*, Coll. Vol. 1, 2nd edn., p. 19, note 5). No attempt was made to separate the individual components of the mixed trimethyladipic acids (147 g.).

αaγ-Trimethylglutaric Acid.—The crude mixture of trimethyladipic acids (147 g.) and manganese carbonate (12·7 g.) was heated at 230—240° until no more material distilled. The distillate was washed with sodium carbonate solution and dried, to give a mixture of 2 : 2 : 4- and 2 : 4 : 4-trimethyl*cyclo*pentanones (42 g.). No attempt was made to separate the components. Birch and Johnson (*J.*, 1951, 1493) have however recently reported the isolation of the pure compounds from a similar mixture. The mixture of ketones (40 g.) was added slowly to a well-stirred suspension of ammonium metavanadate (400 mg.) in 50% nitric acid (214 c.c.) at 90°. Then the mixture was kept at 100° for 1 hr. and finally refluxed for 30 min. The dark residue which remained after removal of the nitric acid was recrystallised from light petroleum (b. p. 60—80°) to give 20·6 g. of αaγ-trimethylglutaric acid, m. p. 97—98° (Found : C, 55·3; H, 8·2. Calc. for $C_8H_{14}O_4$: C, 55·2; H, 8·1%). The monoanilide had m. p. 164—165°. Auwers and Meyer (*Ber.*, 1890, **23**, 293) and Auwers (*Annalen*, 1896, **292**, 224) report m. p.s of 97° and 165° for the acid and anilide respectively. A further amount (7·2 g.) of the pure acid was obtained on acidification of the sodium carbonate washings of the distillate from the pyrolysis.

αaγ-Trimethylglutaric acid has been synthesised previously by the action of finely divided silver on ethyl α-bromo*iso*butyrate (Auwers and Meyer, *Ber.*, 1889, **22**, 2011). We have repeated the synthesis using this procedure and confirmed that the yield is too low to make it practicable for our purposes.

Monoethyl Ester Chlorides of αγγ- and αaγ-Trimethylglutaric Acid (IX).—αaγ-Trimethylglutaric acid (10 g.) was converted in quantitative yield into the anhydride, m. p. 92—93° (Found : C, 61·4; H, 7·69. Calc. for $C_{18}H_{12}O_3$: C, 61·5; H, 7·73%), by refluxing acetyl chloride (12·2 c.c.) in 1 hr. The anhydride (11·35 g.) and absolute ethanol (4·5 c.c.) were heated together, with exclusion of moisture, under reflux at 104° for 5 hr. The mixture was diluted with ether and washed thoroughly with 10% sodium hydrogen carbonate solution. The alkaline extract was made acid to Congo-red with hydrochloric acid and extracted with ether. Removal of the ether from the dried extract left a colourless oil (14·2 g.). This was distilled, to give a main fraction (12·6 g.), b. p. 130—131°/2 mm., n_D^{20} 1·4358 (Found : C, 59·4; H, 9·0. Calc. for $C_{10}H_{18}O_4$: C, 59·4; H, 9·0%). No attempt was made to separate the isomeric ethyl hydrogen esters.

A mixture of acid esters (26 g.) and freshly purified thionyl chloride (40 c.c.) was set aside overnight at room temperature. Excess of thionyl chloride was removed under reduced pressure and the colourless oil remaining was distilled, to give a main fraction (23·1 g.), b. p. 104—106°/4 mm. (Found : Cl, 15·7. Calc. for $C_{10}H_{17}O_3Cl$: Cl, 16·1%).

3 : 7-*Diethoxycarbonyl*-5 : 5-*dimethyloctane*-2 : 4-*dione* (X) ***and* 3 : 7-*Diethoxycarbonyl*-2 : 4-*dimethyloctane*-2 : 4-*dione*.**—The mixed isomeric chlorides obtained in the previous experiment (8·1 g.), in dry benzene (100 c.c.), were added gradually, with stirring, to ethyl sodioacetoacetate (from ethyl acetoacetate, 4·78 g., and sodium 0·84 g.) in benzene (100 c.c.). The temperature was kept at 4°. Then the mixture was set aside at room temperature for 14 hr. and finally refluxed for 2 hr. After cooling, more benzene was added and the mixture was extracted with

10% sodium hydrogen carbonate solution (2 × 25 c.c.). The benzene solution was dried and evaporated. When the residue was treated with successive portions of 10% aqueous sodium carbonate, the bulk dissolved slowly. The product (10·84 g.), isolated from the alkaline solution by acidification and extraction with ether, was distilled. The main fraction (8·75 g.), b. p. 132—135°/1·5 mm., was a colourless oil which gave an intense orange-red colour with ferric chloride solution (Found : C, 61·1; H, 8·5. Calc. for $C_{14}H_{24}O_6$: C, 61·1; H, 8·34%). Absorption in EtOH : $\lambda_{max.}$ 278 mμ (log ε 3·58).

1 : 5-*Diethoxycarbonyl*-3 : 3- (XI) *and* -3 : 5-*dimethylhexan*-2-*one*.—Sodium (0·713 g.) was added in small pieces to a solution, in anhydrous methanol (25 c.c.), of the esters (9·71 g.) obtained in the previous experiment. The mixture was cooled in ice until the addition was complete and then kept at room temperature for 12·5 hr. The clear yellow solution was poured into 2N-hydrochloric acid (200 c.c.). The oil which separated was extracted with ether. The residue after evaporation of the ether was distilled, to give a main fraction (4·3 g.), b. p. 100—102°/0·3 mm. (Found : C, 59·8; H, 8·63. Calc. for $C_{14}H_{24}O_5$: C, 61·7; H, 8·9%). Absorption in EtOH : $\lambda_{max.}$ 251 mμ (log ε 3·2). This product gave a red colour with ferric chloride solution. The analysis indicates that some methyl ester has been formed by ester exchange (cf. Hunsdiecker, *loc. cit.*).

4 : 4 : 6-*Trimethylcyclohexane*-1 : 3-*dione*.—The product from the previous experiment (2·92 g.), in dry ether (40 c.c.), was added to freshly prepared sodium methoxide (from 0·324 g. of sodium). After 30 min. the ether was removed and the residue kept at 100° for 1·5 hr. and at room temperature for 10 hr. Water (50 c.c.) was added and the insoluble product (1·78 g.) was extracted with ether. When the alkaline, aqueous solution was saturated with carbon dioxide, a white precipitate separated slowly. The *dione* recrystallised from light petroleum (b. p. 60—80°) as white needles (31 mg.), m. p. 131—132° (Found : C, 69·7; H, 8·7. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%). Absorption in EtOH : $\lambda_{max.}$ 255 mμ (log ε 4·08). When this product was mixed with the compound $C_9H_{14}O_2$ obtained by Cahn *et al.* (*loc. cit.*) by hydrolysis of angustione, there was no depression of m. p.

2-*Acetyl*-4 : 4 : 6-*trimethylcyclohexane*-1 : 3-*dione* (VI).—A mixture of the foregoing dione (517 mg.), acetic anhydride (2·5 c.c.), and fused sodium acetate (100 mg.) was heated at 130—135° for 3 hr., then cooled, dissolved in ether, and extracted with 10% potassium hydroxide solution (4 × 15 c.c.). The alkaline extract was acidified and extracted with ether. This ether extract was concentrated to 100 c.c., shaken for 15 min. with excess of saturated aqueous copper acetate, and then set aside for 12 hr. The residue obtained on evaporation of the ethereal extract was recrystallised from water–ethanol, to yield unchanged dione and a copper salt, m. p. 203—204°, undepressed in admixture with the copper salt of (±)-angustione (Found : C, 58·6; H, 6·6; Cu, 12·1. Calc. for $C_{11}H_{18}O_3$,0·5Cu : C, 58·2; H, 6·7; Cu, 14·0%). (±)-Angustione was regenerated from the copper salt (30 mg.) by treatment with dilute sulphuric acid (10 c.c.). Its identity was confirmed by the preparation of the piperonylidene derivative, m. p. and mixed m. p. 166—167°.

Infrared Absorption Spectra.—Dehydroangustione (liquid) : strong bands at 5·95, 6·05, 6·40, 6·72, 6·80, 7·20; medium bands at 3·30, 3·35, 7·70, 9·70, 9·95, 11·30; weak bands at 8·05, 8·50, 9·22, 9·25, 10·35, 10·65, 11·83, 12·7, 13·5.

4 : 6 : 6-Trimethyl*cyclo*hex-4(?)-ene-1 : 3-dione (potassium bromide pellet) : strong bands at 3·30, 3·77, 5·97, 6·25, 6·45, 6·7, 6·85, 7·08, 7·25, 7·50, 7·68, 8·10, 8·20, 8·37; medium bands at 3·20, 3·58, 3·83, 9·80, 10·70, 11·07; weak bands at 8·83, 8·95, 9·25, 11·65, 13·30, 14·35.

Aminodehydroangustione (in $CHCl_3$) : strong bands at 6·13, 6·3, 6·82, 7·25, 7·52; medium bands at 2·85, 3·03, 3·30, 5·97, 7·85, 11·25; weak bands at 8·35, 8·78, 9·57, 9·78, 10·00, 10·32, 11·47, 11·83, 12·00.

Ozonolysis of Aminodehydroangustione.—An ice-cold solution of pure aminodehydroangustione (204 mg.; m. p. 151°) in purified chloroform (10 c.c.) was treated with a slow stream of ozonised oxygen (6% of ozone) for 3·5 hr. The ozonisation vessel was followed by a wash-bottle containing water (10 c.c.) to collect volatile products. The chloroform solution was evaporated and the residue treated with the aqueous solution in the wash-bottle together with further water (25 c.c.). The mixture was heated under reflux on a steam-bath for 1 hr. and then distilled into ice-water (10 c.c.) until only 5 c.c. remained. M-Sodium acetate (10 c.c.), N-hydrochloric acid (10 c.c.), and dimedone (0·45 g.) dissolved in sufficient ethanol were added to the distillate which was then heated on a water-bath for 10 min. and then left at room temperature for 12 hr. The dried precipitate (19·2 mg.) had m. p. and mixed m. p. with authentic formaldehyde–dimedone condensation product, 184—186°. This represents a yield of 6·22% of one mole of formaldehyde.

Ozonolysis of Dehydroangustione.—When dehydroangustione (267 mg.) was subjected to

ozonolysis according to the conditions of Caldwell and Jones (*J.*, 1946, 599), 10·3 mg. of formaldehyde–dimedone condensation product were obtained. This represents a yield of 2·5% of one mole of formaldehyde.

We are very grateful to Sir John Simonsen, F.R.S., for his continued interest and for making available samples of angustione and dehydroangustione and their derivatives. One of us (W. R. C.) acknowledges with thanks the award of a Geddes-Grant Research Fellowship and a grant from Messrs. Roche Products Ltd.

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3-*Methyl- and* 3-*Ethyl*-2-2′-*pyridylindole.*

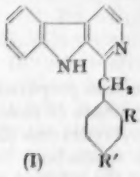
By YEE-SHENG KAO and Sir ROBERT ROBINSON.

[Reprint Order No. 6324.]

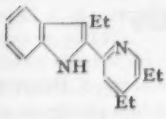
Some preliminary work bearing on the synthesis of alstyrine included the preparation of 3-methyl- and 3-ethyl-2-2′-pyridylindole. The substances resemble alstyrine (corynanthyrine) in ultraviolet absorption and in a new characteristic colour reaction. Before the constitution of alstyrine was known some 2-*cyclo*hexylmethyl-β-carbolines isomeric with that degradation product were synthesised by standard methods.

THE present work was initiated in 1948 (Y.-S. Kao, D.Phil. Thesis, Oxford, 1950) when we were able to examine a specimen of alstyrine kindly provided by Dr. T. M. Sharp of the Wellcome Research Laboratories. This was obtained colourless after chromatography and showed no fluorescence in acid solution. Nevertheless we synthesised certain isomeric 2-*cyclo*hexylmethyl-β-carbolines (I), partly with a view to examining their behaviour in contact with dehydrogenating agents.

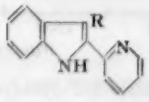
However, in 1949, Karrer and Enslin (*Helv. Chim. Acta*, 1949, **32**, 1390; cf. *idem, ibid.*, 1950, **33**, 100) showed that corynanthyrine (= alstyrine) has the constitution (II) and this caused us to consider the preparation of alstyrine by the obvious application of the Fischer indole-derivatives synthesis.



(I)



(II)



(III)

The introduction of the ethyl group into the 4-position of 5-ethyl-2-methylpyridine by an adaptation of Wibaut's methods (*Rec. Trav. chim.*, 1942, **61**, 59; 1947, **66**, 236; 1948, **87**, 545) succeeded, but the yield was very unfavourable. Hence we turned to 5-ethyl-2-methylpyridine itself as a starting point. This could be converted into 5-ethyl-2-styrylpyridine and the latter oxidised to 5-ethylpyridine-2-carboxylic acid (Prostenik and Filipovic, *Arhiv Kemi*, 1946, **18**, 3). Again we were anticipated here by Anderson, Clemo, and Swan (*J.*, 1954, 2962) who synthesised de-ethylalstyrine (alstyrine less the ethyl group in position 4 of the pyridine nucleus), a degradation product of corynantheine. As the yield of 4 : 5-diethyl-2-methylpyridine was unsatisfactory, we have investigated some 2-phenylpyridine derivatives substituted in positions 3 and 4 in such a way that later conversion of the groups into ethyl groups might be feasible. The project was to nitrate the diethylphenylpyridine, reduce the nitro-group, and oxidise the benzene ring to carboxyl.

Difficulties were encountered in implementing this scheme, which was set aside in favour of other work.

The 2-acylpyridines required for the synthesis of (III; R = Me and Et) were made by distillation of the mixed calcium salts of picolinic and propionic (or butyric) acid. The

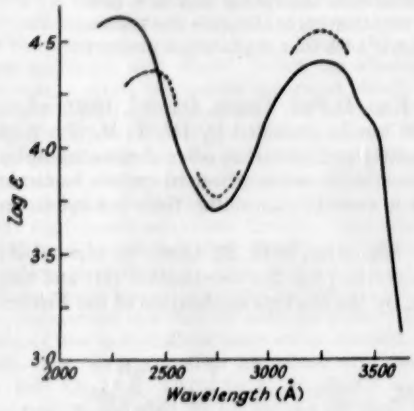
only merit of this process was that it saved time; the alternative adopted by Anderson, Clemo, and Swan (*loc. cit.*) is superior in all other respects.

The ultraviolet absorption spectrum (see Figure) of the 2-2′-pyridylindoles is not much affected by the nature of the alkyl substituents.

At the time of writing the interest taken in these bases in this laboratory has increased, because certain degradation products of ajmaline and its derivatives appear to be substituted 2-2′-pyridylindoles. The synthetical aspect is now being further studied.

Experimental

Alstyrine.—A sample kindly provided by Dr. T. M. Sharp (pale yellow crystals; 0·1 g.) was dissolved in benzene (5 c.c.), adsorbed on an alumina column (6 g.), and eluted with benzene (20 c.c.). The residue obtained on evaporation recrystallised from a little alcohol as colourless plates, m. p. 112—113°. The following colour reaction has been noted. A few crystals of alstyrine were covered with freshly distilled methyl sulphate, and the mixture was gently heated. The yellow product was shaken with benzene and a little water. The aqueous solution gave a red colour on the addition of aqueous sodium hydroxide. The synthetic lower homologues of alstyrine described below gave this characteristic reaction.



Ultraviolet absorption spectra of (—) *3-methyl-2-2′-pyridylindole and* (– – –) *alstyrine.*

3-Methyl-2-2′-pyridylindole (III; R = Me).—Ethyl 2-pyridyl ketone was prepared by the dry distillation of a mixture of crude calcium picolinate and calcium propionate (2 mols.). The ketone, b. p. 202—207° (3·7 g.), in ether (30 c.c.) was mixed with phenylhydrazine (2·5 g.) in ether (5 c.c.). The whole was kept overnight and then heated on the steam-bath for a few minutes. The ether was distilled off until crystallisation commenced and the solution was then cooled. The product (3·7 g.) had m. p. 140—142° after recrystallisation from alcohol (Pinner, *Ber.*, 1901, **34**, 4237, reported the m. p. 140—143°) (Found: C, 74·6; H, 6·2. Calc. for $C_{14}H_{12}N_2$: C, 74·6; H, 6·7%).

A solution of this phenylhydrazone (3 g.) in alcohol (100 c.c.) was saturated with hydrogen chloride at 0°. The mixture was kept at the room temperature for 2 hr., and then refluxed on the steam-bath for 1 hr. The sparingly soluble, yellow hydrochloride, together with ammonium chloride, separated after 20 min. The whole was then concentrated to about 50 c.c. under reduced pressure; abundant separation of long, yellow needles occurred. The solids were washed with alcoholic hydrogen chloride and then with a little alcohol. Concentration of the mother-liquor gave a further crop. The product was dissolved in hot water and the clear yellow, cold solution made alkaline with sodium hydroxide, whereupon the *base* separated as a crystalline mass, an ethereal solution of which was dried and concentrated to about 10 c.c. Long, prismatic needles (0·5 g.), m. p. 104—105°, separated. The mother-liquor afforded 1·4 g. of pale yellow material which, crystallised from alcohol, has m. p. 104—105°. After adsorption on alumina and elution with benzene the m. p. of the colourless, prismatic needles was still 104—105° (Found: C, 80·5; H, 5·8; N, 13·4. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·4%).

The *hydrochloride* crystallised from water and from ethanol as yellow needles, m. p. 250—260°,

giving intense yellow solutions (Found : C, 68·8; H, 5·1. $C_{14}H_{13}N_2Cl$ requires C, 68·7; H, 5·4%). The *picrate* crystallised from ethanol, in which it is sparingly soluble, as elongated, yellow plates, m. p. 206—207° (Found : C, 54·6; H, 3·3. $C_{20}H_{15}O_7N_5$ requires C, 54·9; H, 3·5%). The methiodide was prepared by heating the base and an excess of methyl iodide in a little boiling acetone for several hours. The crystalline residue left after evaporation was recrystallised from methanol and then from ethanol, giving large, orange prisms, m. p. 205—206° (Found : C, 51·8; H, 4·2. $C_{14}H_{12}N_2.CH_3I$ requires C, 51·4; H, 4·3%).

3-*Ethyl-2-2'-pyridylindole* (III; R = Et).—Crude propyl 2-pyridyl ketone (3·3 g.; b. p. 217—223°) was prepared by the dry distillation of a mixture of calcium picolinate and calcium butyrate. Without further purification the ketone was mixed with ether (20 c.c.) and phenylhydrazine (2·4 g.). The solution was kept overnight, and then concentrated on the steam-bath and the sides of the vessel rubbed with a glass rod. When crystallisation commenced, the mixture was cooled and filtered and the solid (1·6 g.) washed with ether until almost colourless; it had m. p. 90—92° (Engler and Majmon, *Ber.*, 1891, **24**, 2536, report m. p. 82°); a further 1·3 g. were obtained from the mother-liquor. An alcoholic solution of the phenylhydrazone was saturated with hydrogen chloride at 0°, kept at room temperature for 2 hr., and then refluxed on the steam-bath for 1 hr. The difficultly soluble hydrochloride, together with ammonium chloride, separated after ½ hr. The greater part of the alcohol was removed under diminished pressure and the mixture was cooled and kept until crystallisation was complete. The product was washed with a little alcoholic hydrogen chloride, dissolved in hot water containing a few drops of hydrochloric acid, and made alkaline with sodium hydroxide. The *base* was collected by means of ether and recrystallised twice from ethanol. It formed large prisms, m. p. 75—76° (Found : C, 80·8; H, 6·5; N, 12·7. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·4; N, 12·6%).

The *hydrochloride* crystallised from ethanol in small, yellow needles, m. p. 219—220° (Found : C, 69·1; H, 6·0. $C_{15}H_{15}N_2Cl$ requires C, 69·6; H, 5·8%). It gave yellow solutions which became turbid on dilution with water. The *picrate* crystallised from ethanol in yellow plates, m. p. 205° (Found : C, 55·9; H, 3·6. $C_{21}H_{17}O_7N_5$ requires C, 55·9; H, 3·8%). The *methiodide*, prepared in acetone as above, was thoroughly washed with acetone and crystallised from ethanol as yellow prisms, m. p. 206—207° (decomp.) (Found : C, 52·6; H, 4·5. $C_{15}H_{14}N_2.CH_3I$ requires C, 52·8; 4·7%).

2-*Methyl-6-phenylpyridine-3* : 4-*dicarboxylic Acid.*—(*a*) A solution of ethyl benzoylpyruvate (44 g.) and ethyl β-aminocrotonate (26 g.) in ether (80 c.c.) was kept at 0° for 24 hr. and at room temperature for a further 24 hr. Large crystals were deposited, which were washed with a little ether. The *substance* melted at 113—114° with vigorous decomp. (Found : C, 61·8; H, 6·7; N, 3·8. $C_{18}H_{23}O_6N$ requires C, 61·8; H, 6·6; N, 4·0%). Mumm and Böhme (*Ber.*, 1921, **54**, 726) state that this adduct has m. p. 148°.

On recrystallisation from methanol or ethanol, in which solvents the substance is difficultly soluble, only a small amount of the material, m. p. 142—143° (decomp.), was recovered (Found : C, 61·9; 6·9; N, 3·6%).

From the alcoholic mother-liquor, on concentration, long needles of the condensation product, m. p. 74—75°, were obtained (see below).

The ethereal filtrate, after removal of the adduct, was evaporated to dryness, leaving a semi-crystalline mass (40 g.), which was combined with the addition product and heated at 130° for 1 hr. Smooth separation of water occurred. The residue was cooled and on crystallisation from ethanol gave white, silky rods (25 g.), m. p. 74—75° (Found : C, 69·1; H, 6·3; N, 4·0. Calc. for $C_{18}H_{19}O_4N$: C, 69·0; H, 6·1; N, 4·4%).

(*b*) Ethyl benzoylpyruvate (22 g.) and ethyl β-aminocrotonate (13 g.) were fused together at about 30° and then kept at the room temperature for 24 hr. Some heat was evolved at first; after 4—5 hr., the whole crystallised. A sample washed with a little ethanol had m. p. 113° (decomp.). The solid was ground with a little ethanol, collected, dried, and then heated at 130°. The product (13 g.) had m. p. 74—75°. This ester was hydrolysed with 10% methanolic potassium hydroxide, at just below the b. p. for 2 hr. The sparingly soluble potassium salt separated after 10 min. Next day the solid was collected, washed with methanol and with ether, and dissolved in a little water, and the solution acidified to Congo-red with hydrochloric acid. The white crystalline acid which separated was washed with water and crystallised from aqueous formic acid, giving white, prismatic needles, m. p. 219° (decomp.) (Found : C, 65·1; H, 4·5; N, 5·5. Calc. for $C_{14}H_{11}O_4N$: C, 65·4; H, 4·3; N, 5·4%). When heated with resorcinol an orange-brown melt was produced and this dissolved in aqueous sodium hydroxide to a cherry-red solution, exhibiting an intense green fluorescence.

The *phenylimide* was obtained in quantitative yield by boiling the dicarboxylic acid with

aniline for 10 min. It was crystallised from benzene and then from ethanol, in which it is sparingly soluble, and obtained as long rods, m. p. 192—193° (Found : C, 76·2; H, 4·6. $C_{20}H_{14}O_2N_2$ requires C, 76·4; H, 4·5%).

2-Methyl-6-phenyl-3 : 4-di(hydroxymethyl)pyridine.—A solution of ethyl 2-methyl-6-phenylpyridine-3 : 4-dicarboxylate (15 g.) in ether (100 c.c.) was added dropwise with stirring during 2 hr. to an ethereal solution (200 c.c) of lithium aluminium hydride (*ca.* 8·5 g.) (prepared according to Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199) with usual precautions. An insoluble double compound separated as a viscous oil, and heat was evolved. The stirring was continued for a further ½ hr. Then, with external ice-cooling, ether, saturated with water, was added with stirring, followed by water and finally 10% aqueous sodium hydroxide (300 c.c.). The ethereal layer was dried and evaporated (residue, 10 g., chiefly unchanged ester). The filtered aqueous layer was extracted twice with chloroform (200 c.c.). After concentration of the solution slender colourless needles separated, having m. p. about 95° with softening from 80°. The material collected from the aqueous layer was extracted with hot water and, on cooling, long needles separated, and these showed the same behaviour on heating. The substance is soluble in hot water, hot chloroform, alcohol, and dilute hydrochloric acid, and is difficultly soluble in ether. It crystallises from water, aqueous methanol, or benzene–ethyl acetate, in all cases as fine needles, without a sharp m. p. The *picrate* crystallised from methanol as stout, yellow rods, m. p. 174—175° (decomp.) (Found : C, 52·6; H, 4·1; N, 12·4. $C_{20}H_{18}O_9N_4$ requires C, 52·4; H, 4·0; N, 12·2%).

Ethyl 3-Acetyl-2-methyl-6-phenylpyridine-4-carboxylate.—A mixture of ethyl benzoylpyruvate (22 g.) and 4-aminopent-3-en-2-one (10 g.) was kept for 4 days. Alcoholic picric acid (22 g. ; 50 c.c.) was then added ; large, yellow prisms (7 g.), m. p. 288° (decomp.), consisting of ammonium picrate separated during 2 days (Found : C, 29·6; H, 2·4; N, 22·7. Calc. for $C_6H_6O_7N_4$: C, 29·3; H, 2·4; N, 22·8%). The alcoholic filtrate was concentrated and the residue shaken with aqueous ammonia and ether. The ethereal layer was washed with aqueous ammonia, dried, and evaporated, leaving a residue, which was triturated with a little alcohol. The white needles so obtained had m. p. 65—66°, unchanged on recrystallisation from ethanol (Found : C, 72·0; H, 6·3; N, 4·7. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·0; N, 4·9%). A further quantity of the *pyridine derivative* was recovered from the mother-liquor (total, 6·5 g.). It is readily soluble in ether, moderately readily soluble in alcohol and hot light petroleum. A somewhat better yield was obtained when a mixture of the generators was kept for 10 days and anhydrous sodium sulphate added after 4 days.

3-Acetyl-2-methyl-6-phenylpyridine-4-carboxylic Acid.—The foregoing ester (2 g.) was hydrolysed by 10% methanolic potassium hydroxide (8 c.c.). The separated potassium salt (long, white needles) was dissolved in water (5 c.c.), acetic acid (1 c.c.) added, and the mixture extracted with ether. Evaporation of the dried extract left a viscous liquid containing some acetic acid, which was washed with a little water by decantation, and the product crystallised from 50% formic acid, from which it separated very slowly as rhombic needles. The air-dried substance had m. p. 163—164·5° after slight softening (Found : C, 70·1; H, 5·1; N, 5·4. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1; N, 5·5%). The methanolic mother-liquor was worked up to yield more of the same *acid* (total, 1·0 g.).

An aqueous solution of iodine was added to the keto-acid (0·6 g.) dissolved in dioxan (20 c.c.) and 10% aqueous sodium hydroxide (6 c.c.) until iodine remained in excess. After 3 hours' heating on the steam-bath the solution was concentrated to about 15 c.c., acidified with a slight excess of sulphuric acid (the precipitate formed redissolved), and filtered from a gum. Sodium hydroxide solution was added until the precipitate redissolved, and the solution was carefully acidified until no more turbidity appeared. The product crystallised on concentration of a dried ethereal solution. It was recrystallised from aqueous formic acid, and had m. p. 219° (decomp.) alone or mixed with 2-methyl-6-phenylpyridine-3 : 4-dicarboxylic acid.

1 : 6-Dihydro-3 : 2′-dimethyl-6-oxo-1 : 6′-diphenylpyridino(3′ : 4′-4 : 5)pyridazine.—Equivalent quantities of ethyl 3-acetyl-2-methyl-6-phenylpyridine-4-carboxylate and phenylhydrazine were heated in a little ethanol on the steam-bath for ½ hr. After trituration with a little ether the crystals were collected, washed with ether, and recrystallised from benzene and from ethanol ; the *base* formed long, white needles, m. p. 182—183°, sparingly soluble in ethanol (Found : C, 77·1; H, 4·8; N, 13·0. $C_{21}H_{17}ON_3$ requires C, 77·0; H, 5·2; N, 12·9%).

Similarly with hydrazine the keto-ester afforded *1 : 6-dihydro-3 : 2′-dimethyl-6-oxo-6′-phenylpyridino(3′ : 4′-4 : 5)pyridazine* which is sparingly soluble in most solvents but crystallised from ethanol (0·5 g. in 100 c.c.) ; it had m. p. 261—262° (Found : C, 7·1; H, 5·0; N, 17·1. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2; N, 16·7%).

4 : 5-*Diethyl-2-methyl-* and 4 : 5-*diethyl-2-styrylpyridine Picrates*.—Zinc dust (35 g.) (activated by acid, washed with water and acetone, and dried *in vacuo*) was added during 3 hr. to a mixture of acetic anhydride (170 c.c.) and 5-ethyl-2-methylpyridine (50 g.) which was vigorously stirred at 50°. Acetic acid (35 c.c.) was added, and another portion of zinc (15 g.) was added gradually, after which the solution was refluxed for 2 hr. The basified solution was steam-distilled and a litre of distillate was collected. This was acidified with hydrochloric acid and concentrated to about 150 c.c. The *base* was then set free and isolated by means of ether. About 28 g. of recovered 5-ethyl-2-methylpyridine distilled up to 200°. Further distillation under diminished pressure gave fractions : (3·0 g.) b. p. 74—80°/25 mm., (1·0 g.) b. p. 88—102°/25 mm., and the desired 4 : 5-diethyl derivative (2·5 g.), b. p. 102—104°/25 mm. (Found : 78·8; H, 10·2; N, 9·4. Calc. for $C_{10}H_{15}N$: C, 80·5; H, 10·3; H, 9·4%). The base (0·5 g.) was mixed with picric acid (1 g.) in ethanol (6 c.c.), giving a yellow crystalline *picrate* (0·5 g.) which, recrystallised thrice from ethanol, had m. p. 165—167° (Found : C, 51·2; H, 4·8; N, 14·7. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%).

A mixture of the crude 4 : 5-diethyl-2-methylpyridine (2·0 g.), benzaldehyde (5 c.c.), and zinc chloride (1 g.) was refluxed under nitrogen for 4 hr. The yellow product (0·5 g.), isolated in the known manner, did not solidify. From alcohol–ether solution it gave a *picrate* which, thrice recrystallised from methanol, formed yellow prisms, m. p. 143—144° with previous softening (Found : C, 59·3; H, 4·8; N, 11·6. $C_{22}H_{22}O_7N_4$ requires C, 59·2; H, 4·8; N, 12·0%).

3-(2-cyclo*Hexylacetamidoethyl*)*indole*.—A mixture of tryptamine hydrochloride (1·0 g.) and powdered potassium carbonate (2·1 g.) was suspended in ether (20 c.c.) and gently refluxed for ½ hr. *cyclo*Hexylacetyl chloride (0·92 g.) in ether (100 c.c.) was then added during an hour and refluxing continued for 8 hr. Evaporation of the ethereal solution left a viscous oil which solidified when rubbed. The solid (1·2 g.) was dissolved in benzene (charcoal), and the filtered solution concentrated to about 5 c.c., whereupon white needles, m. p. 82—83°, were deposited on keeping (0·5 g.). A further portion (0·1 g.) was obtained from the mother-liquor. The *amide* crystallised from aqueous methanol as colourless needles, m. p. 82—83° (Found : C, 75·2, 76·7; H, 8·5, 8·5; N, 9·7. $C_{18}H_{24}ON_2$ requires C, 76·1; H, 8·4; N, 9·9%).

2-cyclo*Hexylmethyl*-4 : 5-*dihydro*-β-*carboline*.—Phosphoric anhydride (7 g.) was gradually added, during 45 min., to a hot solution of 3-(2-*cyclo*hexylacetamidoethyl)indole (0·9 g.) in toluene (40 c.c.). The toluene layer was decanted and treated with another equal quantity of phosphoric anhydride as before. The combined solid residues were decomposed with ice and water, concentrated hydrochloric acid (5 c.c.) was added, and the whole digested on the steam-bath until the aqueous layer became clear. The gum that remained was treated with further dilute hydrochloric acid. The combined acid solution (200 c.c.) was washed with ether and then made strongly alkaline with potassium hydroxide. The mixture was extracted twice with ether, and the ethereal layer dried and concentrated to a small volume; fine needles (50 mg.) separated, m. p. 166—169° to a turbid oil becoming completely clear at 174°. The ethereal mother-liquor was evaporated to dryness, leaving pale yellow crystals (0·1 g.) of the *carboline* which, after two recrystallisations from methanol, had m. p. 172—174° with previous softening (Found : C, 81·0; H, 8·4. $C_{18}H_{22}N_2$ requires C, 81·1; H, 8·3%). A dilute acidic solution exhibited a strong green fluorescence.

The *methiodide* was prepared in acetone. The solution at once developed a green fluorescence and was kept for a day; on slow evaporation, large greenish prisms separated, having m. p. 238—240° (Found : C, 55·8; H, 6·3. $C_{18}H_{22}N_2,CH_3I$ requires C, 55·9; H, 6·2%).

2-cyclo*Hexylmethyl*-β-*carboline* (I; R = R′ = H).—*cyclo*Hexylmethyldihydro-β-carboline (140 mg.) and selenium (70 mg.) were heated together at 300° for 10 min. The light brown melt was extracted repeatedly with ether. The ethereal solution which showed a strong fluorescence was concentrated to about 2 c.c. Four-sided plates, m. p. 195—197° (40 mg.), separated. In order to remove a trace of selenium which caused discoloration, a solution of the crystals in ether (15 c.c.) was filtered through a kieselguhr column and then concentrated to a small volume. The colourless crystals which separated had m. p. 198—199°; and m. p. 200° after recrystallisation from methanol (Found : C, 81·5; H, 7·5; N, 10·4. $C_{18}H_{20}N_2$ requires C, 81·8; H, 7·6; N, 10·6%).

The *picrate* crystallised from ethanol in yellow, prismatic needles, m. p. 250—261° (Found : C, 58·7; H, 4·8. $C_{24}H_{23}O_7N_5$ requires C, 58·4; H, 4·7%). The *methiodide*, prepared in acetone, formed large, yellow prisms which, recrystallised from acetone, had m. p. 260° (decomp.), after softening from 250° (Found : C, 56·9; H, 5·9. $C_{19}H_{20}N_2,CH_3I$ requires C, 56·1; H, 5·7%).

3-[2-(4′-*Methyl*cyclo*hexylacetamido*)*ethyl*]*indole*.—Tryptamine (0·5 g.; m. p. 113°; freshly prepared from its hydrochloride) was intimately mixed with 4-methyl*cyclo*hexylacetic acid

(0·5 g.) and heated at 180—190° for ½ hr. The melt darkened slightly and solidified on cooling. It was crushed and repeatedly triturated with ether. A small amount (0·2 g.) of insoluble crystalline material remained (soluble in water and probably tryptamine methyl*cyclo*hexylacetate) and the ethereal solution was filtered (charcoal) and evaporated to dryness. The residue (0·7 g.) crystallised from benzene as prismatic needles, m. p. 68—75° with softening from 60° and becoming completely clear at 80° (Found: C, 76·3; H, 8·3; N, 9·4. $C_{19}H_{26}ON_2$ requires C, 76·5; H, 8·8; N, 9·4%).

2-(4′-*Methyl*cyclo*hexylmethyl*)-β-*carboline* (I; R = H, R′ = Me).—Phosphoric anhydride (15 g.) was added portionwise to a gently boiling solution of 3-[2-(4′-methyl*cyclo*hexylacetamido)-ethyl]indole (1·5 g.) in benzene (40 c.c.), and the solid cake broken up from time to time with a glass rod. After 45 min., the benzene was decanted and the residue washed several times with benzene (a considerable amount of unchanged amide could be recovered from the benzene). The phosphoric complex was decomposed by crushed ice, concentrated hydrochloric acid (5 c.c.) was added, and the whole digested on the steam-bath until a clear solution resulted. The solution was then decanted from the insoluble gum, which was again treated with hydrochloric acid as before. The combined acid solution was washed with ether and made alkaline with potassium hydroxide. The liberated base, isolated by means of ether, crystallised from light petroleum as long, pale yellow needles, m. p. 157—159° with softening from 150°. The substance closely resembled the lower homologue and was submitted to dehydrogenation without further purification.

The dihydro-carboline (0·2 g.) was intimately mixed with selenium (0·1 g.) and heated with stirring at 295—300° for 10 min. The dark cake was broken up and repeatedly triturated with ether. The extract was filtered through kieselguhr to remove colloidal selenium, and then concentrated to a small volume, from which crystals separated (50 mg.). The *compound* recrystallised from a little methanol as colourless prisms, m. p. 204—205° (Found: C, 82·0; H, 8·4. $C_{19}H_{22}N_2$ requires C, 81·9; H, 8·0%). The *picrate* crystallised from ethanol as yellow needles, m. p. 235—236° (Found: C, 58·9; H, 5·0. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0%).

2-*Methyl*cyclo*hexylacetic Acid*.—It was found that ethyl 1-hydroxy-2-methyl*cyclo*hexylacetate (Auwers and Ellinger, *Annalen*, 1912, **397**, 230) was most conveniently dehydrated by treatment with thionyl chloride and pyridine at 0° in ether. The product had b. p. 120—122°/35 mm. The unsaturated ester was hydrogenated over Adams catalyst and hydrolysed. 2-Methyl*cyclo*hexylacetyl chloride (by thionyl chloride) had b. p. 105—106°/35 mm. With ammonia it furnished the amide which crystallised from benzene in glistening needles, m. p. 155—156°, unchanged by recrystallisation. For the amide of this acid (made in a different manner), Wallach (*Annalen*, 1912, **394**, 322) gave m. p. 160—161° and Mousseron and Winternitz (*Bull. Soc. chim. France*, 1946, 604) gave m. p. 149—150°.

3-[2-(2′-*Methyl*cyclo*hexylacetamido*)*ethyl*]*indole*.—This compound was prepared by condensing tryptamine with either 2-methyl*cyclo*hexylacetyl chloride or with the acid itself. The product (crude, m. p. 105—108°), when recrystallised twice from benzene, formed colourless, prismatic needles, m. p. 110—111° (Found: C, 76·1; H, 8·7; N, 9·3. $C_{19}H_{26}ON_2$ requires C, 76·4; H, 8·8; N, 9·4%).

4 : 5-*Dihydro*-2-(2′-*methyl*cyclo*hexylmethyl*)-β-*carboline*.—Phosphoric anhydride (10 g.) was added to a solution of the above tryptamide (1·0 g.) in refluxing benzene (40 c.c.) during 1½ hr., and the whole refluxed for another 2 hr. The *product* was worked up as in the previous examples and eventually crystallised from ether as elongated prisms, m. p. 190—192° (Found: C, 81·0; H, 8·6; N, 10·5. $C_{19}H_{24}N_2$ requires C, 81·4; H, 8·6; N, 10·0%).

2-(2′-*Methyl*cyclo*hexylmethyl*)-β-*carboline* (I; R = Me, R′ = H).—The preceding base (0·14 g.) and selenium (70 mg.) were heated at 295—300° for 10 min. with constant stirring. The *product*, isolated as above, crystallised from ethanol as prismatic needles, m. p. 215° (Found: C, 81·9; H, 7·5; N, 10·4. $C_{19}H_{22}N_2$ requires C, 82·0; H, 8·0; N, 10·1%). The acid solutions of this base exhibited the usual blue-violet fluorescence. The *picrate* crystallised from ethanol as greenish-yellow prisms, m. p. 233—234° (Found: C, 59·4; H, 5·1. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0%).

We are grateful to the British Council for a Scholarship awarded to one of us (Y.-S. K.) and to Professor P. Karrer for a specimen of corynanthyrine (alstyrine).

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Lactones. Part II. The Structure of Mellein.*

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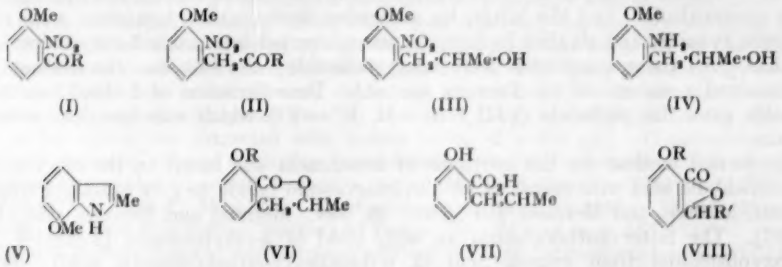
Mellein (ochracin) is shown to be (−)-3 : 4-dihydro-8-hydroxy-3-methyl-*iso*coumarin by the synthesis of its (±)-methyl ether (cf. *Chem. and Ind.*, 1955, 93). Two new syntheses of *iso*ochracin confirm its structure as 3-ethyl-7-hydroxyphthalide.

WHEN the fungus *Aspergillus melleus* Yukawa is grown on a medium containing sucrose (Nishikawa, *J. Agric. Chem. Soc. Japan*, 1933, **9**, 772) or maltose (Burton, *Nature*, 1950, **165**, 274) mellein is produced. Yabuta and Sumiki (*J. Agric. Chem. Soc. Japan*, 1934, **10**, 703) have shown that mellein is identical with ochracin, a metabolic product of *A. ochraceus* (*idem*, *ibid.*, 1933, **9**, 1264). Chemical studies on mellein (Nishikawa, *ibid.*, 1933, **9**, 1059; Yabuta and Sumiki, *locc. cit.*) indicate that mellein must have either structure (VI; R = H) or (VIII; R = H, R′ = Et). Tamura (*ibid.*, 1939, **15**, 685) has claimed a synthesis of the latter compound, 3-ethyl-7-hydroxyphthalide, which was identical with *iso*ochracin [formed by the action of hot sulphuric acid on melleic acid (VII) which is produced by mild alkali fusion of mellein (Yabuta and Sumiki, *loc. cit.*, 1934)]. Tamura's synthesis, further discussed below, was ambiguous in that the structural assignment of the product was entirely dependent on the degradative studies on mellein. Mellein has been given the phthalide structure or the related hydroxy-acid formulation in two recent reviews on mould products (Raistrick, *Proc. Roy. Soc.*, 1949, *A*, **199**, 141; Aghoramurthy and Seshadri, *J. Sci. Ind. Res., India*, 1954, **13**, *A*, 114); more recently Birch and Donovan (*Chem. and Ind.*, 1954, 1047) have favoured the structure (VI; R = H) on chemical and biogenetic grounds but cite no additional experimental support. We therefore considered it desirable to confirm that mellein has structure (VI; R = H) by a direct synthetical approach.



The starting material for this work was 3-methoxy-2-nitrobenzoic acid (I; R = OH) (Ewins, *J.*, 1912, **101**, 544) which was converted by the Arndt–Eistert procedure into 3-methoxy-2-nitrophenylacetic acid (II; R = OH), previously prepared from 3-methoxy-2-nitrotoluene by the oxalation method (Blaikie and Perkin, *J.*, 1924, **125**, 296). The acid chloride (II; R = Cl), obtained as described by Barger and Schlittler (*Helv. Chim. Acta*, 1932, **15**, 381), was transformed by the ethoxymagnesiomalonate method *via* the intermediate ethyl 3-methoxy-2-nitrophenylacetylmalonate into 3-methoxy-2-nitrophenylacetone (II; R = Me). This nitro-ketone on reduction with sodium borohydride gave a high yield of 1-(3-methoxy-2-nitrophenyl)propan-2-ol (III) which on hydrogenation over nickel afforded the amine (IV). If 3-methoxy-2-nitrophenylacetone is hydrogenated over nickel, 7-methoxy-2-methylindole (V) is formed in good yield. Diazotisation of the amine, conversion into the nitrile (which was not purified), and subsequent alkaline hydrolysis gave (±)-3 : 4-dihydro-8-methoxy-3-methyl*iso*coumarin (VI; R = Me), m. p. 66—67°. The compound gave an intermediate m. p. on admixture with (−)-mellein

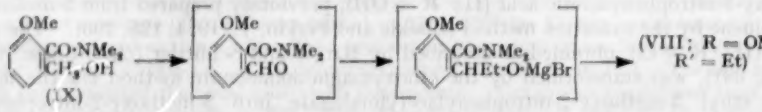
* Part I, *J.*, 1955, 708.

methyl ether, m. p. 88—89°, and the ultraviolet and infrared absorption spectra of both compounds (the latter in CCl_4) were identical. The carbonyl stretching frequencies of both compounds in solution (1741 cm.$^{-1}$) and in the solid state (1716 cm.$^{-1}$) when compared with those of 7-methoxyphthalide (Duncanson, Grove, and Zealley, *J.*, 1953, **1331**) in the same solvent (1782 cm.$^{-1}$) and in the solid state (1748 cm.$^{-1}$) are consistent with the existence of a six-membered ring in (VI; R = Me). (−)-Mellein methyl ether is recovered after boiling with alkali, no appreciable racemization being detected.

Having established that mellein is (−)-**3**:4-dihydro-8-hydroxy-3-methyl*iso*coumarin (VI; R = H), we directed attention to *iso*ochracin which must be 3-ethyl-7-hydroxyphthalide (VIII; R = H, R′ = Et).

In Tamura's synthesis (*loc. cit.*) of 3-ethyl-7-hydroxyphthalide (VIII; R = H, R′ = Et) the first stage consisted in the condensation of 3-nitrophthalic anhydride with sodium propionate and propionic anhydride to give 3-ethylidene-7-nitrophthalide. We have been unable to repeat this work and this, together with recent experiences in the orientation of products of the Doebner reaction of 3-methoxy- (Kuhn and Dury, *Chem. Ber.*, 1951, **84**, 848; Hochstein and Pasternack, *J. Amer. Chem. Soc.*, 1952, **74**, 3905) and 3-nitro-phthalic anhydride (*loc. cit.*) in which the condensations went in the opposite direction from those described by Tamura, made it desirable to synthesise *iso*ochracin by an unambiguous method, and in fact two such methods have been developed. In the first, an obvious analogy with the use of 2-amino-3-methoxyacetophenone in the synthesis of 7-methoxy-3-methylphthalide (VIII; R = H, R′ = Me) by Kushner, Morton, Boothe, and Williams (*J. Amer. Chem. Soc.*, 1953, **75**, 1097) suggested the corresponding propiophenone as a starting material. Though in our hands attempts to nitrate *m*-methoxypropiophenone were unsuccessful, 3-methoxy-2-nitropropiophenone (I; R = Et) was obtained from 3-methoxy-2-nitrobenzoyl chloride by application of the ethoxymagnesiomalonate method to give ethyl 3-methoxy-2-nitrobenzoylmalonate (not isolated), which was *C*-methylated; the product on hydrolysis and decarboxylation gave the ketone (I; R = Et), a useful extension of Walker and Hauser's reaction. 3-Methoxy-2-nitropropiophenone was reduced by sodium borohydride to the corresponding nitro-alcohol which was hydrogenated to the amino-alcohol, and the latter, by successive diazotisation, treatment with nickel potassium cyanide, and alkaline hydrolysis, was converted into crude 3-ethyl-7-methoxyphthalide. All these compounds were uncrystallisable; the last was chromatographed but remained a viscous oil (cf. Tamura, *loc. cit.*). Demethylation of 3-ethyl-7-methoxyphthalide gave the phthalide (VIII; R = H, R′ = Et) which was identical with *iso*ochracin.

The second method for the synthesis of *iso*ochracin was based on the reaction of a phthalaldehydic acid with excess of an alkylmagnesium halide to give a 3-alkylphthalide (Simonis, Marben, and Mermod, *Ber.*, 1905, **38**, 398; Mermod and Simonis, *ibid.*, 1906, **39**, 897). The latter authors claim an 86% yield of 3-ethylmeconin (3-ethyl-6:7-dimethoxyphthalide) from opianic acid (5:6-dimethoxyphthalaldehydic acid); in our hands a very low yield was obtained in this reaction with high recovery of the acid. We attribute the failure of this reaction to the low solubility of opianic acid in ether; therefore,



the ether-soluble 6-formyl-2:3-dimethoxy-*NN*-dimethylbenzamide, the intermediate in the preparation of opianic acid by the method of Blair, Brown, and Newbold (*J.*, 1955, 708), was treated with an excess of the appropriate Grignard reagent; acid hydrolysis of the products gave 3-methyl- and 3-ethyl-meconin in good yields. Application of this method starting from 6-hydroxymethyl-2-methoxy-*NN*-dimethylbenzamide (IX) (Blair, Brown, and Newbold, *loc. cit.*) gave in good yield 3-ethyl-7-methoxyphthalide which on demethylation gave 3-ethyl-7-hydroxyphthalide (*iso*ochracin).

A comparison between the ultraviolet absorption spectrum above 2200 Å of mellein

with those of certain 7-hydroxyphthalides is given in the Table. The strong bathochromic shift of the maxima in mellein compared with the positions of those in the phthalides is noteworthy and might be of diagnostic use in deciding between isomeric 3 : 4-dihydro*iso*coumarin and phthalide structures.

Compound	Solvent	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
Mellein [a]	EtOH	2460	6500	3140	4100
*iso*Ochracin [a]	EtOH	2340	7000	3000	4600
7-Hydroxy-3-methylphthalide [b]	MeOH	2320	7500	2980	4700
7-Hydroxyphthalide [c]	EtOH	2320	8700	2990	4600

[a] This paper; [b] Hochstein and Pasternack (*loc. cit.*); [c] Blair, Brown, and Newbold (*loc. cit.*).

Experimental

Ultraviolet spectra were determined in ethanol.

* 3-*Methoxy-2-nitrobenzoyl Chloride*.—3-Methoxy-2-nitrobenzoic acid (9·0 g.; Ewins, *loc. cit.*) was refluxed with redistilled thionyl chloride (60 c.c.) for 2 hr. Excess of reagent was removed under reduced pressure, benzene added to the residue, and this likewise removed, both operations conducted at bath-temperature $< 40°$. The solid residue was kept *in vacuo* overnight over sodium hydroxide, the crude product being used directly for the next stage. A specimen, crystallised from anhydrous ether, gave 3-*methoxy-2-nitrobenzoyl chloride* as needles, m. p. 85° (Found: C, 44·7; H, 2·55. $C_8H_6O_4NCl$ requires C, 44·6; H, 2·8%). The acid chloride decomposes on storage.

* *Diazomethyl* 3-*Methoxy-2-nitrophenyl Ketone*.—A solution of diazomethane in ether (250 c.c.) [from methylnitrosourea (33 g.)] was treated with a solution of 3-methoxy-2-nitrobenzoyl chloride (9·0 g.) in dioxan (30 c.c.) with agitation at 0°, and kept overnight at room temperature. Removal of the solvent under reduced pressure gave the diazo-ketone (9·0 g.). Crystallisation from dioxan gave *diazomethyl* 3-*methoxy-2-nitrophenyl ketone* as prisms, m. p. 144° (decomp.) (Found: C, 49·2; H, 3·45. $C_9H_7O_4N_3$ requires C, 48·9; H, 3·2%). Light absorption: Max. at 2160 (ε 24,000), 2480 (ε 18,400) and 2980 Å (ε 10,400).

* 3-*Methoxy-2-nitrophenylacetic Acid*.—A solution of the foregoing diazo-ketone (9·0 g.) in warm dioxan (75 c.c.) was added in portions during 20 min. to a stirred mixture of freshly prepared silver oxide (4·0 g.) in distilled water (150 c.c.) in which sodium thiosulphate (3·0 g.) and anhydrous sodium carbonate (5·0 g.) had been dissolved, the temperature being kept at 50—60°. After a further hour at 50—60° the temperature was raised to 90—95° for ½ hr. and then the mixture was filtered and the filtrate diluted with water (200 c.c.), acidified with dilute nitric acid, and extracted with chloroform (3 × 200 c.c.). The combined chloroform extracts were washed with water (50 c.c.) and dried (Na_2SO_4). Removal of the chloroform gave a tar which was extracted with boiling water (2 × 100 c.c.). Concentration of the combined extracts, followed by cooling, gave 3-*methoxy-2-nitrophenylacetic acid* (6·05 g.) which separated from water (charcoal) as needles, m. p. 136—137° (Found: C, 51·2; H, 4·2. Calc. for $C_9H_9O_5N$: C, 51·2; H, 4·3%). Light absorption: Max. at 2090 (ε 13,000), 2540—2600 (ε 2800), and 3000 Å (ε 1800). Blaikie and Perkin (*loc. cit.*) give m. p. 137—138°.

Ethyl 3-*Methoxy-2-nitrophenylacetylmalonate*.—3-Methoxy-2-nitrophenylacetic acid (4·22 g.) was converted into the acid chloride as described by Barger and Schlittler (*loc. cit.*) and a solution of the latter compound in ether (25 c.c.) added during 10 min. to refluxing ethereal ethyl ethoxymagnesiomalonate, prepared from ethyl malonate (3·52 g.) as prescribed in *Org. Synth.*, **30**, 70. A thick viscous oil was formed and heating was continued for ½ hr. until stirring became difficult. The cooled mixture was shaken with dilute sulphuric acid (2·5 g. in 20 c.c. of water) until the oily magnesium complex had dissolved. The ethereal phase was separated, washed with water, dried (Na_2SO_4), and evaporated, to give the crude product (6·0 g.) which solidified. A specimen, crystallized from aqueous ethanol, gave *ethyl* 3-*methoxy-2-nitrophenylacetylmalonate* as fine needles, m. p. 85—86° (Found: C, 54·4; H, 5·2. $C_{16}H_{19}O_8N$ requires C, 54·4; H, 5·4%). Light absorption: Max. at 2060 (ε 16,000) and 2500 Å (ε 7250).

3-*Methoxy-2-nitrophenylacetone*.—Crude ethyl 3-methoxy-2-nitrophenylacetylmalonate (5·7 g.) in acetic acid (12 c.c.), sulphuric acid (1·5 c.c.; *d* 1·84), and water (8 c.c.) was refluxed for 6 hr.; evolution of carbon dioxide was then no longer apparent. The cooled solution was made alkaline with 5N-sodium hydroxide and extracted with ether (3 × 50 c.c.). The combined ethereal extract was washed with water, dried (Na_2SO_4), and evaporated, to give an oil which rapidly solidified. Crystallisation from aqueous ethanol gave 3-*methoxy-2-nitrophenylacetone*

* Dr. J. J. Brown assisted in experiments marked thus.

(2·0 g.) as long needles, m. p. 61—62° (Found : C, 57·6; H, 5·15. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3%). Light absorption : Max. at 2060 (ε 15,800), 2650 (ε 1500), and 2900—3060 Å (ε 1200).

7-Methoxy-2-methylindole.—3-Methoxy-2-nitrophenylacetone (1·2 g.) in ethyl acetate (100 c.c.) was shaken at room temperature and atmospheric pressure in hydrogen in the presence of Raney nickel (1 g.; W6, *Org. Synth.*, **29**, 25). Absorption was rapid, and complete after ½ hr. The filtered solution was evaporated under reduced pressure and the residue crystallized from light petroleum (b. p. 40—60°), to give *7-methoxy-2-methylindole* (900 mg.) as long needles, m. p. 83—85° (Found : C, 74·6; H, 6·4. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8%). Light absorption : Max. at 2200 (ε 50,000) and 2650 Å (ε 9000). The *picrate* separated from aqueous methanol as fine red needles, m. p. 153° (Found : C, 48·85; H, 3·42. $C_{16}H_{14}O_9N_4$ requires C, 49·2; H, 3·6%). Light absorption : Max. at 2220 (ε 45,000), 2380—2420 (ε 13,400), and 3570 Å (ε 16,200). 7-Methoxy-2-methylindole dissolves in warm 5N-hydrochloric acid, being recovered on basification of the solution; in benzene solution, on treatment with aqueous-ethanolic *p*-dimethylaminobenzaldehyde hydrochloride, it gives a violet-red colour, indistinguishable from that given by 2-methylindole (Ehrlich's reaction).

1-(3-Methoxy-2-nitrophenyl)propan-2-ol.—A solution of 3-methoxy-2-nitrophenylacetone (1·0 g.) in ethanol (30 c.c.) and water (10 c.c.) was kept at room temperature for 2 hr. with sodium borohydride (750 mg.), then diluted with water (100 c.c.) and extracted with chloroform (3 × 50 c.c.). The dried (Na_2SO_4) extract was evaporated and the residue crystallized from benzene–light petroleum (b. p. 60—80°), to give the *alcohol* (900 mg.) as needles, m. p. 82—83° subliming at 70°/0·001 mm. (Found : C, 56·8; H, 6·4. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·2%). Light absorption : Max. at 2140 (ε 11,600), 2720 (ε 1550), and inflexion at 2360—2460 Å (ε 1700).

1-(2-Amino-3-methoxyphenyl)propan-2-ol.—The foregoing alcohol (500 mg.) in ethyl acetate (50 c.c.) was shaken at room temperature and atmospheric pressure in hydrogen with the above Raney nickel catalyst (0·5 g.) until absorption was complete (5 min. with fresh catalyst). The filtered solution was evaporated under reduced pressure and the residue crystallized from light petroleum (b. p. 40—60°), to give the *amine* (400 mg.) as needles, m. p. 69° subliming at 60°/0·001 mm. (Found : C, 66·4, H, 8·6. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3%). Light absorption : Max. at 2120 (ε 21,000), 2380 (ε 6600), and 2860 Å (ε 2500).

3 : 4-Dihydro-8-methoxy-3-methylisocoumarin.—A solution of the foregoing amino-alcohol (300 mg.) in hydrochloric acid (0·43 c.c.; *d* 1·16) and water (9 c.c.) was diazotised with a solution of sodium nitrite (120 mg.) in water (1 c.c.) at 0°. After neutralization with sodium carbonate the diazonium solution was added to one of potassium cyanide (380 mg.), nickel chloride (300 mg.), and anhydrous sodium carbonate (100 mg.) in water (10 c.c.) at 15° with stirring, kept for 2 hr., and heated at 70° for 15 min. The cooled reaction solution was extracted with ether (3 × 20 c.c.), and the combined, dried (Na_2SO_4) extracts were evaporated, to give a gum which was treated with aqueous potassium hydroxide (20 c.c.; 10%) and refluxed for 3 hr. The solution was acidified (Congo-red) and extracted with chloroform (3 × 25 c.c.); evaporation of the dried (Na_2SO_4) extract gave a gum which slowly solidified. Crystallization from light petroleum (b. p. 40—60°) gave *3 : 4-dihydro-8-methoxy-3-methylisocoumarin* (60 mg.) as prisms, m. p. 66—67° (Found : C, 68·7; H, 6·6. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). Light absorption : Max. at 2120 (ε 28,000), 2440 (ε 7400), and 3050 Å (ε 4700).

Mellein Methyl Ether.—Mellein (26 mg.), m. p. 56—57° (lit., m. p. 58°), having absorption max. at 2120 (ε 20,000), 2460 (ε 6500), and 3140 Å (ε 4100), was kept in excess of ethereal diazomethane at room temperature for 3 days. The solution was evaporated, the residual gum taken up in benzene (5 c.c.), the solution filtered through a column of Grade II alumina (3 × 1 cm.), and the column washed with benzene (200 c.c.). Evaporation of the combined eluates and crystallization of the solute from light petroleum (b. p. 60—80°) gave mellein methyl ether (18 mg.) as prisms, m. p. 88—89° (lit., 88—89°), $[\alpha]_D^{15}$ −245°, −250° (*c*, 1·1, 0·5 in $CHCl_3$). A mixture with the synthetic lactone had an intermediate m. p. Light absorption : Max. at 2130 (ε 27,000), 2430 (ε 7200), and 3050 Å (ε 4500).

Attempted racemization. Mellein methyl ether (11 mg.) was refluxed for 6 hr. with 3N-sodium hydroxide (5 c.c.). Acidification and isolation, by means of chloroform, followed by crystallization from light petroleum (b. p. 60—80°), gave starting material (8 mg.) as prisms, m. p. and mixed m. p. 86—88°, $[\alpha]_D^{15}$ −240° (*c*, 0·4 in $CHCl_3$).

3-Methylmeconin.—6-Hydroxymethyl-2 : 3-dimethoxy-*NN*-dimethylbenzamide (2·0 g.) was prepared and oxidised with chromic acid as described by Blair, Brown, and Newbold (*loc. cit.*) and the resulting crude aldehyde in ether (10 c.c.) treated at 15° with the Grignard reagent prepared from methyl iodide (1·42 g.) and magnesium (250 mg.) in ether (10 c.c.). The mixture was refluxed for 1 hr., cooled, treated with hydrochloric acid (100 c.c.; 3N), and refluxed for

1½ hr. The cooled mixture was extracted with ether (3 × 100 c.c.), and the combined extracts were washed with water, 10% aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Evaporation of the ether and crystallization of the residue from benzene–light petroleum (b. p. 60—80°) gave 3-methylmeconin (60%) as prismatic needles, m. p. 101° (subliming at 100°/0·001 mm.) and not depressed on admixture with a specimen prepared in 5% yield by the method of Simonis, Marben, and Mermod (*loc. cit.*) (Found: C, 63·0; H, 6·0. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%). Light absorption: Max. at 2150 (ε 29,000) and 3060 Å (ε 4300). By the same method, except that ethylmagnesium bromide was used, 3-ethylmeconin was prepared in 70% yield; it separated from aqueous ethanol as short prisms, m. p. 98° (Found: C, 65·1; H, 6·3. Calc. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35%). Light absorption: Max. at 2140 (ε 27,500) and 3080 Å (ε 4000). Mermod and Simonis (*loc. cit.*) give m. p. 98°.

3-*Methoxy*-2-*nitropropiophenone*.—By the technique described above for the preparation of ethyl 3-methoxy-2-nitrophenylacetylmalonate, 3-methoxy-2-nitrobenzoyl chloride (4·4 g.) was converted into crude ethyl 3-methoxy-2-nitrobenzoylmalonate (5·5 g.). This semi-solid was dissolved in ethanolic sodium ethoxide [from sodium (0·5 g.) and ethanol (10 c.c.)], methyl iodide (2 c c.) was added, and the solution refluxed for 3 hr. during which methyl iodide (2 c.c.) was added in four portions. The cooled solution was diluted with water and extracted with ether (3 × 15 c c.), and the combined ethereal extracts were washed with water and dried (Na_2SO_4). Removal of the ether gave a gum which was treated as described in the preparation of 3-methoxy-2-nitrophenylacetone, to give 3-methoxy-2-nitropropiophenone (1·1 g.) which separated from aqueous ethanol as small needles, m. p. 96° subliming at 80°/0·001 mm. (Found: C, 57·3; H, 5·1. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3%). Light absorption: Max. at 2120 (ε 22,000), 2340—2400 (ε 5800), and 3080 Å (ε 2500).

3-*Ethyl*-7-*hydroxyphthalide*.—(*a*) 6-Hydroxymethyl-2-methoxy-*NN*-dimethylbenzamide (290 mg.) was oxidized as described by Blair, Brown, and Newbold (*loc. cit.*) and the resulting crude aldehyde in ether (20 c.c.) treated with ethereal ethylmagnesium bromide prepared from ethyl bromide (0·54 g.) and magnesium (0·12 g.) in ether (6 c.c.). A precipitate was formed immediately and the mixture was refluxed for 10 min., cooled, and treated with 3N-hydrochloric acid (40 c.c.), the ether distilled off, and the aqueous solution refluxed for ½ hr. The cooled solution was extracted with chloroform (3 × 50 c.c.), and the combined extracts were washed with water (25 c.c.), dried (Na_2SO_4), and evaporated to give a viscous oil, which did not crystallize even after filtration in benzene solution through Grade II alumina. The gum was refluxed with aqueous hydrobromic acid (20 c.c.; *d* 1·46) in a stream of coal-gas for 1 hr. The cooled solution was diluted with water (20 c.c.) and extracted with chloroform (4 × 50 c.c.), and the combined extracts were dried (Na_2SO_4) and evaporated to a brown resin. The latter was extracted with boiling light petroleum (b. p. 60—80°) (4 × 50 c.c.), and the combined extracts were concentrated to *ca.* 2 c.c. and kept at 0°. The resulting solid recrystallized from light petroleum (b. p. 40—60°), to give 3-ethyl-7-hydroxyphthalide (75 mg.) as needles, m. p. 78° subliming at 75°/0·001 mm. (Found: C, 67·2; H, 6·1. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·7%). The compound was undepressed in m. p. on admixture with a specimen of *iso*ochracin, m. p. 78° (lit., 78—79°), prepared from mellein according to Yabuta and Sumiki's method (*J. Agric. Chem. Soc. Japan*, 1934, **10**, 703). It gives a violet colour with ferric chloride in aqueous ethanol. Light absorption: Max. at 2140 (ε 18,400), 2340 (ε 7000), and 3000 Å (ε 4600).

(*b*) By the method described above for the preparation of 1-(3-methoxy-2-nitrophenyl)-propan-2-ol, 3-methoxy-2-nitropropiophenone (700 mg.) was reduced to the corresponding alcohol, a viscous oil, which was hydrogenated as given for its analogue. The product, a viscous oil, was converted into the oily 3-ethyl-7-methoxyphthalide by the method described above for the formation of 3 : 4-dihydro-8-methoxy-3-methyl*iso*coumarin. The crude methoxy-phthalide was demethylated with boiling aqueous hydrobromic acid as in (*a*), to give 3-ethyl-7-hydroxy-phthalide (20 mg.) which separated from light petroleum (b. p. 40—60°) as needles, m. p. 77—78° alone or mixed with preparation (*a*).

We are indebted to Dr. H. S. Burton for the generous gift of a sample of mellein, to Mr. J. F. Grove and Dr. L. A. Duncanson for the infrared data, to Dr. J. J. Brown for assistance, and to Messrs. T. and H. Smith, Ltd., for gifts of chemicals.

The Royal Technical College, Glasgow. [*Received, April 15th*, 1955.]

Steroids and Walden Inversion. Part XXVI. 4β-Methoxycholest-5-ene, 6β-Methoxycholest-4-ene, and Related Compounds.*

By D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers.

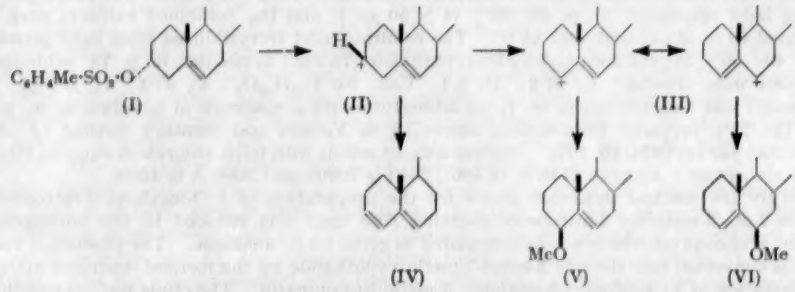
[Reprint Order No. 6339.]

4β-Methoxycholest-5-ene and 6β-methoxycholest-4-ene have been prepared and shown to be identical with the products isolated from the methanolysis of *epi*cholesteryl toluene-*p*-sulphonate by Evans and Shoppee (*J.*, 1953, 540).

Hydrogenation of cholest-5-en-4β-ol, its acetate, and its methyl ether gave by hydrogenolysis only cholestane, whereas hydrogenation of cholest-5-en-4α-ol gave cholestan-4α-ol. Hydrogenation of the epimeric 6-acetoxy- and 6-hydroxycholest-4-enes gave respectively the epimeric 6-acetoxycoprostanes or the epimeric coprostan-6-ols; the latter by cautious oxidation both yielded coprostan-6-one, isomerised by acid, alkali, or alkaline aluminium oxide to cholestan-6-one.

Reduction of 5-hydroxycholestan-4-one with sodium–*n*-propanol gave the expected products, cholestan-4α-ol and cholestane-4α : 5-diol; similar reduction of 5-hydroxycholestan-6-one gave cholestan-6α-ol, and cholestane-5 : 6α-diol accompanied by coprostane-5 : 6α-diol.

The methanolysis of *epi*cholesteryl toluene-*p*-sulphonate (I) has been shown independently by Schmid and Kägi (*Helv. Chim. Acta*, 1952, **35**, 2194) and Evans and Shoppee (*J.*, 1953, 540) to afford cholesta-3 : 5-diene (IV) and two isomeric methyl ethers regarded as 4β-methoxycholest-5-ene (V) and 6β-methoxycholest-4-ene (VI). The observation that the acetolysis of *epi*cholesteryl toluene-*p*-sulphonate exhibits first-order kinetics (Williams and Shoppee, *J.*, 1955, 686) supports, by analogy, Evans and Shoppee's view (*loc. cit.*) that the methanolysis involves a unimolecular heterolysis to give the cation (II), which can achieve neutrality by loss of a proton to give cholesta-3 : 5-diene (IV), or by rearrangement involving hydrogen migration to yield the mesomeric cation (III), and thence the isomeric methyl ethers (V) and (VI).

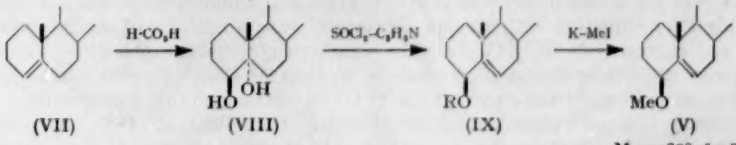


The partial syntheses of these methyl ethers, now reported, confirm Evans and Shoppee's structural conclusions.† The cause of the β-configurational specificity displayed, which recalls that of the 3 : 5-*cyclo*steroid rearrangement, is obscure, but some analogies are provided by the oxidation of cholesterol with sodium dichromate in benzene–acetic acid to 6β-hydroxycholest-4-en-3-one (Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4377; 1954, **76**, 1728), or with selenium dioxide–acetic acid to cholest-5-ene-3β : 4β-diol, which at higher temperatures rearranges to cholest-4-ene-3β : 6β-diol (Rosenheim *et al.*, *J.*, 1937, 377; 1943, 135; Butenandt and Hausmann, *Ber.*, 1937, **70**, 1154; Paige, *J.*, 1943, 437).

* Part XXV, *J.*, 1955, 1891.

† Since this paper was submitted, the partial syntheses of the methyl ethers (V) and (VI) and of related compounds have been described by Becker and Wallis (*J. Org. Chem.*, 1955, **20**, 353).

Hydroxylation of cholest-4-ene (VII) with performic or peracetic acid gave, after mild alkaline hydrolysis, cholestane-4β : 5-diol (VIII), previously obtained by oxidation of cholesta-2 : 4-diene to cholest-2-ene-4β : 5-diol and hydrogenation of the latter (Bergmann and Skau, *J. Org. Chem.*, 1940, **5**, 439). Acetylation with acetic anhydride–pyridine at 20° gave the 4β-monoacetate whilst use of acetyl chloride in boiling chloroform yielded the diacetate; the 4β-monoacetate by dehydration with thionyl chloride–pyridine at 0° gave 4β-acetoxycholest-5-ene (IX; R = Ac), hydrolysed by treatment with lithium aluminium hydride in ether to cholest-5-en-4β-ol (IX; R = H). This by methylation with potassium–



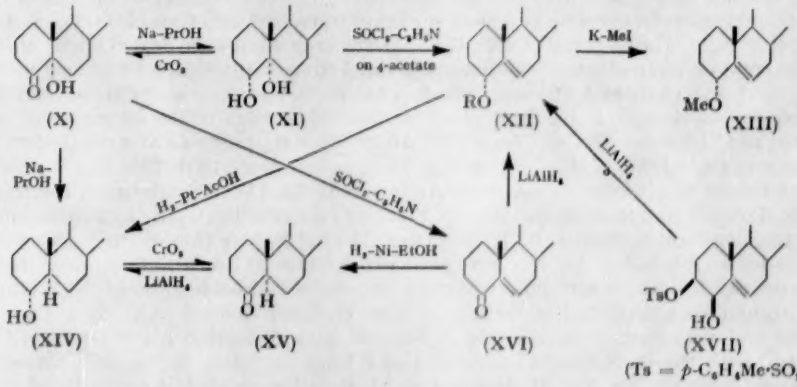
(VII) (VIII) (IX) (V)

M. p. 68°, [−73] * *
M. p. 66°, [−73] *b*
M. p. 65°, [−68]

* These and similar figures in brackets are $[\alpha]_D$.

methyl iodide in benzene gave 4β-methoxycholest-5-ene (V), identical with specimens prepared by Schmid and Kägi (*loc. cit.*; ref. *a*) and by Evans and Shoppee (*loc. cit.*; ref. *b*).

Catalytic hydrogenation with platinum in ethyl acetate with or without a trace of perchloric acid, or in ethanol containing a trace of formic acid, of the alcohol or its acetate (IX; R = H or Ac) caused hydrogenolysis and gave only cholestane; hydrogenation of the acetate (IX; R = Ac) with platinum in dioxan gave an unidentified hydrocarbon, m. p. 66°, $[\alpha]_D$ +1°, which is under investigation. Hydrogenation of the methyl ether (V) has already been reported to give cholestane (Evans and Shoppee, *loc. cit.*; Schmid and Kägi, *loc. cit.*).



(X) (XI) (XII) (XIII)

(XIV) (XV) (XVI) (XVII)

(Ts = *p*-$C_6H_4Me{\cdot}SO_2$)

Hydroxylation of cholest-4-ene (VII) with osmium tetroxide gave cholestane-4α : 5-diol (XI). The 4α-monoacetate of this, obtained by acetic anhydride–pyridine at 20°, was dehydrated by thionyl chloride–pyridine at 0° or on attempted acetylation with acetyl chloride and dimethylaniline in boiling chloroform, affording 4α-acetoxycholest-5-ene (XII; R = Ac), which by contrast with the 4β-epimeride (IX; R = Ac), slowly decomposed at 100° into cholesta-3 : 5-diene and acetic acid, probably by ionic elimination [*E*1], since the 4β-epimeride (IX; R = Ac), by evaporation of an ethereal solution containing 1 drop of 10N-hydrochloric acid, gave cholesta-3 : 5-diene and acetic acid. The 4α-monoacetate (XII; R = Ac) by hydrolysis with lithium aluminium hydride in ether gave cholest-5-en-4α-ol (XII; R = H; OH, equatorial)]. This substance was

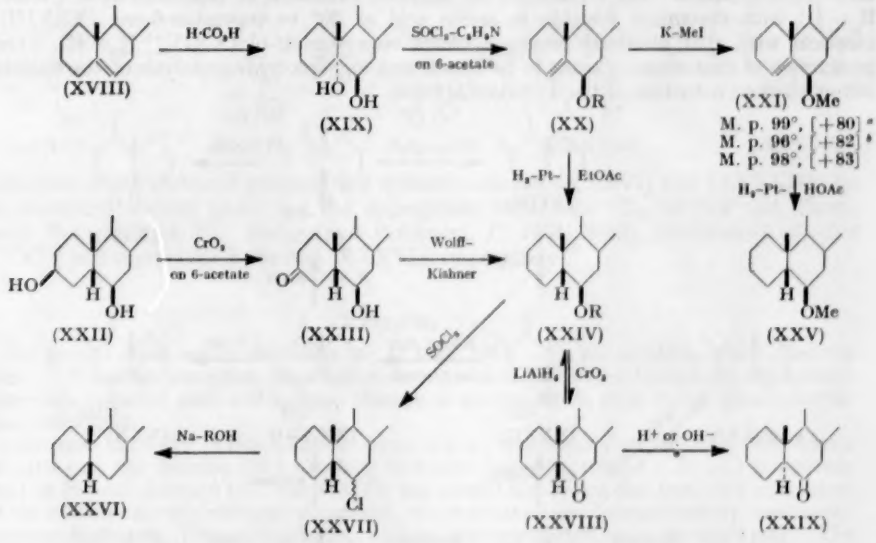
identical with the product of the reduction of 4β-hydroxycholest-5-en-3β-yl toluene-*p*-sulphonate (XVII; 4-OH, axial) with lithium aluminium hydride (Karrer, Sareen, Asmis, and Schwyzer, *Helv. Chim. Acta*, 1951, **34**, 1022); these authors proved the configuration at $C_{(4)}$ of their product by hydrogenation in presence of platinum–acetic acid to cholestan-4α-ol (XIV) [wrongly described in their paper as cholestan-4β-ol] (Tschesche and Hagedorn, *Ber.*, 1935, **68**, 2251; Fürst and Scotoni, *Angew. Chem.*, 1951, **63**, 196; Barton and Rosenfelder, *J.*, 1951, 1032). Methylation with potassium–methyl iodide in benzene gave 4α-methoxycholest-5-ene (XIII), m. p. 85—86° (Schmid and Kägi, *loc. cit.*).

Oxidation of cholestane-4β : 5-diol (VIII) with *N*-bromosuccinimide furnished 5-hydroxycholestan-4-one (X), which by reduction with lithium aluminium hydride gave cholestane-4β : 5-diol, but by reduction with sodium–*n*-propanol gave a mixture of cholestane-4α : 5-diol (XI) and cholestan-4α-ol (XIV), readily separated chromatographically. The latter substance was oxidised by chromium trioxide to cholestan-4-one (XV), which was identical with a specimen prepared from cholest-4-ene (VII) by conversion into 4-nitrocholest-4-ene and reduction of this with zinc–acetic acid (Windaus, *Ber.*, 1920, **53**, 488); by reduction with lithium aluminium hydride it gave cholestan-4β-ol (88%) accompanied by cholestan-4α-ol (XIV) (7%). 5-Hydroxycholestan-4-one (X) was readily dehydrated with thionyl chloride–pyridine at 0° to cholest-5-en-4-one, $\lambda_{max.}$ 242 mμ (log ε 3·85) (XVI), which showed the low extinction characteristic of a cisoid system, and has previously been prepared with $\lambda_{max.}$ 241 mμ (log ε 3·86) from 2α-bromocholestan-3-one by treatment with potassium acetate in acetic acid at 210° (Butenandt and Ruhenstroth-Bauer, *Ber.*, 1944, **77**, 397; cf. Ruzicka, Plattner, and Aeschbacher, *Helv. Chim. Acta*, 1938, **21**, 866). By reduction with Raney nickel in ethanol containing a trace of formic acid cholest-5-en-4-one (XVI) gave cholestan-4-one (XV), and by reduction with lithium aluminium hydride cholest-5-en-4α-ol (XII : R = H).

Cholest-5-ene (XVIII) was hydroxylated with performic acid according to the directions of Reich, Walker, and Collins (*J. Org. Chem.*, 1951, **16**, 1753) to give cholestane-5 : 6β-diol (XIX), which with acetic anhydride–pyridine at 20° gave the 6β-monoacetate and with acetyl chloride in boiling chloroform the diacetate. The 6β-monoacetate on dehydration with thionyl chloride–pyridine at 0° was smoothly converted into 6β-acetoxycholest-4-ene (XX; R = Ac). The 6β-acetate (XX; R = Ac) was unchanged when heated briefly at 100°, but evaporation of an ethereal solution containing 1 drop of 10N-hydrochloric acid yielded acetic acid and cholesta-4 : 6-diene, which is known to rearrange under these conditions to cholesta-3 : 5-diene. It has been observed that 6β-acetates of the *allo*pregnane series (Herzog and Ehrenstein, *J. Org. Chem.*, 1951, **16**, 1050), of the pregn-4-ene series (Balant and Ehrenstein, *ibid.*, 1952, **17**, 1587; Florey and Ehrenstein, *ibid.*, 1954, **19**, 1331), and of the cholest-4-ene series (Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4377; Sondheimer, Kaufmann, Romo, Martinez, and Rosenkranz, *ibid.*, p. 4712) are epimerised at $C_{(6)}$ by hydrogen chloride at 0° in chloroform containing 0·7% of ethanol (but not in pure chloroform); 6β-acetoxycholest-4-ene (XX; R = Ac) was not epimerised by this treatment. 6β-Acetoxycholest-4-ene resisted hydrolysis with hot methanolic potassium hydroxide although by treatment with lithium aluminium hydride in ether it gave cholest-4-en-6β-ol (XX; R = H). The alcohol and potassium–methyl iodide in benzene gave 6β-methoxycholest-4-ene (XXI), identical with the preparations by Schmid and Kägi (*loc. cit.*; ref. *a*) and Evans and Shoppee (*loc. cit.*; ref. *b*). Hydrogenation of 6β-methoxycholest-4-ene with platinum in ethyl acetate–acetic acid gave 6β-methoxycoprostane (XXV), m. p. 64—65°, $[\alpha]_D$ +10°, which was different from 6β-methoxycholestane, double m. p. 52°/77°, $[\alpha]_D$ +14°, prepared from cholestan-6β-ol by methylation with potassium and methyl iodide in boiling benzene.

Hydrogenation of cholest-4-en-6β-ol (XX; R = H) with platinum in ethyl acetate containing perchloric acid (a trace) gave cholestane and coprostan-6β-ol (XXIV; R = H), characterised as the acetate, which showed the infrared spectral pattern associated with an axial steroid acetate with bands at 1730 and 1242 cm.$^{-1}$. Hydrogenation of 6β-acetoxycholest-4-ene (XX; R = Ac) with platinum in ethyl acetate in the presence of a trace of perchloric acid gave cholestane and coprostan-6β-yl acetate (XXIV; R = Ac). The stereochemical course of the hydrogenations (XX ⟶ XXIV) was proved in three ways.

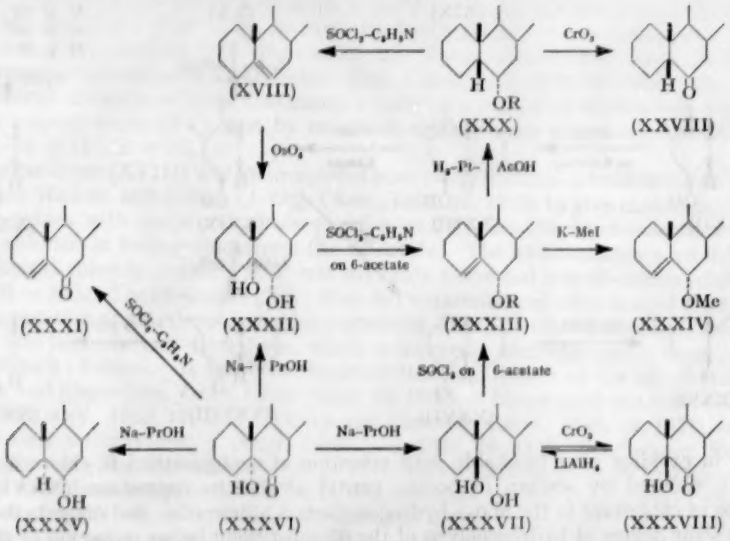
First, the 6-monoacetate of coprostane-3β : 6β-diol (Prelog and Tagmann, *Helv. Chim. Acta*, 1944, **27**, 1880) was oxidised with chromium trioxide in acetic acid at 20° to the 3-oxo-6β-yl acetate which by alkaline hydrolysis gave 6β-hydroxycoprostan-3-one (XXIII); this by modified Wolff–Kishner reduction furnished coprostan-6β-ol (XXIV; R = H). Secondly, by cautious oxidation with chromium trioxide in acetic acid at 20° coprostan-6β-ol afforded coprostan-6-one (XXVIII), m. p. 133—134°, $[\alpha]_D$ −44°, the infrared absorption spectrum of which showed a band at 1705 cm.$^{-1}$ [6-membered-ring ketone of the A/B-*cis*-series (cf. R. N. Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 956)]; coprostan-6-one, when reduced with lithium aluminium hydride, regenerated coprostan-6β-ol, and by treatment with acid or alkali or by contact with moist alkaline aluminium oxide, underwent keto–enol prototropy with inversion of configuration at $C_{(6)}$, to give the more thermodynamically stable cholestan-6-one (XXIX), m. p. 96°, $[\alpha]_D$ −2° (cf. Windaus, *Ber.*, 1920, **53**, 488). Thirdly, coprostan-6β-ol with thionyl



chloride in pyridine gave (probably with retention of configuration) 6ξ-chlorocoprostane (XXVII), reduced by sodium in boiling pentyl alcohol to coprostane (XXVI). The formation of cholestane in the above hydrogenations is noteworthy, and suggests the occurrence to some degree of hydrogenolysis of the 6β-substituent before reduction of the 4 : 5-double bond; the rôle played by the 6β-substituent in the production of compounds of the coprostane series does not appear readily explicable (cf. Brewster, *J. Amer. Chem. Soc.*, 1954, **76**, 6361, 6364, 6368; Fukushima and Gallagher, *ibid.*, 1955, **77**, 139).

Cholest-5-ene (XVIII) by hydroxylation with osmium tetroxide gave cholestane-5 : 6α-diol (XXXII), converted by acetic anhydride–pyridine at 20° into the 6α-monoacetate; use of acetyl chloride–dimethylaniline in boiling chloroform gave the diacetate, which failed to crystallise but by hydrolysis with lithium aluminium hydride regenerated the 5α : 6α-diol (XXXII). The 6α-monoacetate was dehydrated by thionyl chloride–pyridine to 6α-acetoxycholest-4-ene (XXXIII; R = Ac), which gave a yellow colour with tetranitromethane in chloroform (cf. Djerassi, Rosenkranz, *et al.*, *J. Org. Chem.*, 1951, **16**, 192), and which by hydrolysis with potassium hydroxide or lithium aluminium hydride afforded cholest-4-en-6α-ol (XXXIII; R = H). The 6α-acetate (XXXIII; R = Ac) was stable to thermal treatment, but gave cholesta-3 : 5-diene under mild acidic conditions. The allylic alcohol (XXXIII; R = H) was also obtained from cholest-4-en-6-one (XXXI) by reduction with lithium aluminium hydride. Cholest-4-en-6α-ol (XXXIII; R = H)

on attempted methylation with potassium–methyl iodide in boiling benzene yielded cholesta-3 : 5-diene; further experimentation showed that methylation at 30—35° gave, after chromatographic purification, 6α-methoxycholest-4-ene (XXXIV) as an oil, $[\alpha]_D$ +20°, which did not crystallise and decomposed at ~70° to furnish cholesta-3 : 5-diene. This ready elimination* of the 6α-methoxyl group (equatorial) in (XXXIV) contrasts with the relative stability of the 6β-methoxyl group (axial) in (XXI), recalls the ready elimination of the 4α-acetoxyl group (equatorial) in (XI; R = Ac) in contrast to the relative stability of the 4β-acetoxyl group (axial) in (IX; R = Ac), and suggests an ionic mechanism [*E*1]. Cholest-4-en-6α-ol (XXXIII; R = H) by hydrogenation with platinum in ethyl acetate in the presence of a trace of perchloric acid gave some cholestane and coprostan-6α-ol (XXX; R = H); similarly, 6α-acetoxycholest-4-ene (XXXIII; R = Ac) by hydrogenation with platinum in ethyl acetate–acetic acid afforded cholestane accompanied by 6α-acetoxycoprostane (XXX; R = Ac). The stereochemical course of these hydrogenations was established by cautious oxidation of coprostan-6α-ol (XXX; R = H) with chromium trioxide in acetic acid at 20° to coprostan-6-one (XXVIII), identical with that obtained previously from coprostan-6β-ol (XXIV; R = H). The production of cholestane is again to be noted, and suggests hydrogenolysis of the 6α-substituent before reduction of the 4 : 5-double bond.



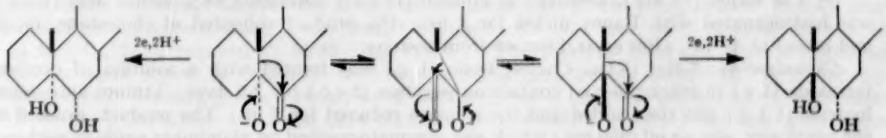
Whereas coprostan-6β-ol (XXIV; OH, axial), on treatment with thionyl chloride–pyridine, underwent substitution to give 6ξ-chlorocoprostane (XXVII), similar treatment of coprostan-6α-ol (XXX; OH, equatorial) gave coprostan-6α-yl sulphite, accompanied by elimination to yield cholest-5-ene (XVIII) in 35% yield. In coprostan-6α-ol, the 6α-hydroxyl group and the 5β-hydrogen atom are both equatorial to ring B, so that although *trans*-orientated these entities cannot be coplanar.

Oxidation of cholestane-5 : 6β-diol (XIX) with *N*-bromosuccinimide (cf. Reich, Walker, and Collins, *loc. cit.*) gave 5-hydroxycholestan-6-one (XXXVI). This ketol was reduced by lithium aluminium hydride to cholestane-5 : 6β-diol (XIX), but with sodium–*n*-propanol to a mixture, separated chromatographically, of cholestan-6α-ol (XXXV) (Tschesche, *Ber.*, 1932, **65**, 1842; Shoppee and Summers, *J.*, 1952, 3361), cholestane-5 : 6α-diol (XXXII), and coprostane-5 : 6β-diol (XXXVII). The last-named by mild oxidation with chromium

* Whilst Fieser (*J. Amer. Chem. Soc.*, 1953, **75**, 4377) observed that both 6α- and 6β-acetoxycholest-4-en-3-one are smoothly converted into cholest-4-en-3-one by treatment with zinc–acetic acid, we find that 6α-acetoxycholest-4-ene is unaltered by this reagent.

trioxide–acetic acid at 20° gave 5-hydroxycoprostan-6-one (XXXVIII), reconverted into the diol (XXXVII) by reduction with lithium aluminium hydride. The non-crystalline 6α-monoacetate of the diol (XXXVII) was dehydrated with thionyl chloride–pyridine at 0° to 6α-acetoxycholest-4-ene (XXXIII; R = Ac); thus the diols (XXXII) and (XXXVII) differ only in configuration at $C_{(5)}$, and their molecular rotations, despite vicinal action, are consistent with these structures.

The conversion of 5-hydroxycholestan-6-one (XXXVI) into coprostane-5 : 6α-diol (XXXVII) is noteworthy. It does not involve prior formation of cholestane-5 : 6α-diol (XXXII) and inversion of configuration at $C_{(5)}$ thereof, because both cholestane-5 : 6α-diol and cholestan-5-ol are unchanged by extended treatment with sodium in boiling *n*-propanol; it therefore involves fission either of the $C_{(5)}$–O bond, or, more probably, of the $C_{(5)}$–$C_{(4)}$ or $C_{(5)}$–$C_{(10)}$ bond * in a reversible α-ketol change (Shoppee, *J.*, 1928, 1662; Wendler and Taub, *Chem. and Ind.*, 1955, 505):



(XXXII) (XXXVI) (XXXVIII) (XXXVII)

Reduction of the carbonyl group of the epimeric α-ketols (XXXVI) and (XXXVIII) by the dissolving sodium gives, *via* the appropriate carbanions $^{-}C_{(6)}$–$O^{-}\}Na^{+}$ (cf. Birch, *Quart. Rev.*, 1952, **4**, 69; Barton and Robinson, *J.*, 1954, 3045), cholestane-5 : 6α-diol (XXXII) and coprostane-5 : 6α-diol (XXXVII) respectively.

Experimental

For general experimental directions, see *J.*, 1955, 1891. $[\alpha]_D$ are in $CHCl_3$ unless otherwise stated. Ultraviolet absorption spectra were determined in EtOH on a Unicam SP 500 spectrometer with corrected scale and infrared absorption spectra in CS_2 on a Perkin–Elmer double-beam instrument.

Cholestane-4β : 5-diol (VIII).—Cholest-4-ene (6·6 g.) was rapidly stirred with 98% formic acid (105 c.c.) and benzene (10 c.c.) whilst hydrogen peroxide (100-vol.; 12 c.c.) was slowly added at 30—45° during 6 hr. The solution was poured into water and extracted with ether, and the ethereal extract dried and evaporated; the residual oil was refluxed with 5% methanolic potassium hydroxide (100 c.c.) for 2·5 hr., and the mixture worked up in the usual way. The product (6·6 g.) was chromatographed on aluminium oxide (200 g.) in pentane; elution with pentane gave cholest-4-ene (1·8 g.), whilst use of ether–benzene (1 : 1; 5 × 100 c.c.) gave cholestane-4β : 5-diol, m. p. 171—172°, $[\alpha]_D$ +27° (*c*, 1·9). The 4β-monoacetate was obtained by use of acetic anhydride in pyridine at 20° for 16 hr. and crystallised from acetone in needles, m. p. 175—176°, $[\alpha]_D$ +38° (*c*, 1·5). The 4β : 5α-diol (120 mg.) was refluxed with acetyl chloride (1·5 c.c.) and dimethylaniline (1·0 c.c.) in purified chloroform (25 c.c.); 4β : 5α-diacetoxycholestane (80 mg.), isolated in the usual way, was an oil but chromatography on aluminium oxide (3 g.) and elution with benzene–pentane (3 : 7) gave 4β : 5-*diacetoxycholestane*, m. p. 147—148°, $[\alpha]_D$ +60° (*c*, 1·7), after recrystallisation from aqueous acetone [Found (after drying at 100°/0·01 mm. for 3 hr.): C, 76·7; H, 10·8. $C_{31}H_{52}O_4$ requires C, 76·2; H, 10·7%].

4β-*Acetoxycholest-5-ene* (IX; R = Ac).—4β-Acetoxycholestan-5-ol (150 mg.) by treatment with thionyl chloride (0·5 c.c.) in pyridine (2 c.c.) at 0° furnished a product, which after chromatography on aluminium oxide by elution with benzene–pentane (1 : 4) yielded 4β-*acetoxycholest-5-ene*, m. p. 108°, $[\alpha]_D$ −70° (*c*, 1·1), after recrystallisation from acetone–methanol (1 : 9) [Found (after drying at 90°/0·01 mm. for 2 hr.): C, 81·4; H, 11·3. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%], giving a yellow colour with tetranitromethane–chloroform.

Cholest-5-en-4β-ol (IX; R = H).—4β-Acetoxycholest-5-ene (350 mg.), dissolved in ether (20 c.c.), was refluxed with a solution of lithium aluminium hydride (400 mg.) in ether (30 c.c.) for 0·5 hr. The solid product (320 mg.) was isolated in the usul way and by recrystallisation

* We are grateful to a Referee for drawing our attention to the possibly analogous cases of the conversion of purpurogallin into purpurogallone and of humulone into humulic acid.

from methanol yielded *cholest-5-en-4β-ol*, m. p. 132°, $[\alpha]_D$ −59° (*c*, 0·44) [Found (after drying at 100°/0·01 mm. for 3 hr.): C, 84·0; H, 12·2. $C_{27}H_{46}O$ requires C, 83·8; H, 12·0%], giving a yellow colour with tetranitromethane–chloroform.

4β-Methoxycholest-5-ene (V).—Cholest-5-en-4β-ol (150 mg.) was heated with "molecular" potassium (~100 mg.) in benzene (25 c.c.) for 1 hr., and then with methyl iodide (5 c.c.) for 3 hr. The product was isolated in the usual way and purified by chromatography on aluminium oxide prepared in pentane; elution with pentane furnished 4β-methoxycholest-5-ene, m. p. 65°, $[\alpha]_D$ −68° (*c*, 0·5), after crystallisation from acetone, giving a yellow colour with tetranitromethane–chloroform and identical with specimens prepared by Evans and Shoppee (*loc. cit.*) and by Schmid and Kägi (*loc. cit.*).

Hydrogenation of Cholest-5-en-4β-ol and its Acetate.—(*a*) The acetate (70 mg.), dissolved in ethyl acetate (10 c.c.), was hydrogenated with platinum oxide (50 mg.) for 2 hr.; the product (68 mg.) consisted solely of cholestane, m. p. and mixed m. p. 77—78° after crystallisation from acetone.

(*b*) The stenol (70 mg.), dissolved in ethanol (15 c.c.) containing 98% formic acid (1 c.c.), was hydrogenated with Raney nickel for 3 hr.; the product consisted of cholestane, m. p. and mixed m. p. 79°, after crystallisation from acetone.

Cholestane-4α : 5-diol (XI).—Cholest-4-ene (1 g.) was treated with a solution of osmium tetroxide (1 g.) in ether (25 c.c.) containing pyridine (2 c.c.) for 2·5 days; lithium aluminium hydride (1·4 g.) was then added and the solution refluxed for 2 hr. The product, isolated in the usual way, was an oil (650 mg.) which was chromatographed on aluminium oxide in pentane. Elution with pentane gave cholest-4-ene (550 mg.), m. p. and mixed m. p. 78° after crystallisation from acetone; elution with ether–benzene (3 : 7) gave *cholestane-4α : 5-diol* (50 mg.), m. p. 135°, $[\alpha]_D$ +14° (*c*, 0·83) [Found (after drying at 100°/0·01 mm. for 3 hr.): C, 80·1; H, 11·8. $C_{27}H_{48}O_2$ requires C, 80·1; H, 11·95%]. The *4α-monoacetate*, obtained by use of acetic anhydride in pyridine at 20° for 18 hr., had m. p. 149°, $[\alpha]_D$ +35° (*c*, 1·28) after recrystallisation from methanol [Found (after drying at 100°/0·01 mm. for 3 hr.): C, 77·9; H, 11·3. $C_{29}H_{50}O_3$ requires C, 77·95; H, 11·3%].

4α-Acetoxycholest-5-ene (XII; R = Ac).—(*a*) Cholestane-4α : 5-diol 4-monoacetate (420 mg.) was treated with thionyl chloride (1 c.c.) in pyrdine (10 c.c.) at 0° for 0·5 hr. to afford, after processing in the usual way, *4α-acetoxycholest-5-ene*, m. p. 123°, $[\alpha]_D$ −27° (*c*, 0·65), after crystallisation from acetone [Found (after drying at 60°/0·01 mm. for 3 hr.): C, 81·0; H, 11·2. $C_{29}H_{48}O_2$ requires C, 81·2; H, 11·3%], giving a yellow colour with tetranitromethane–chloroform. The acetate (150 mg.) when heated at 100° for 10 min., evolved acetic acid; chromatography of the resultant oil on aluminium oxide (4·5 g.) in pentane, with elution by pentane (3 × 15 c.c.), gave cholesta-3 : 5-diene (70 mg.), m. p. and mixed m. p. 77°, after recrystallisation from acetone, whilst elution with benzene–pentane (1 : 9; 4 × 15 c.c.) gave the unchanged acetate (69 mg.), m. p. and mixed m. p. 120—123° after recrystallisation from acetone.

(*b*) Cholestane-4α : 5-diol (275 mg.), refluxed with acetyl chloride (2 c.c.) and dimethylaniline (2 c.c.) in chloroform (15 c.c.), underwent partial acetylation accompanied by dehydration, to yield 4α-acetoxycholest-5-ene (100 mg.), m. p. and mixed m. p. 120—123° with the specimen prepared by method (*a*), after recrystallisation from acetone, and cholestane-4α : 5-diol 4-monoacetate (139 mg.), m. p. and mixed m. p. 148° after recrystallisation from methanol. Separation was effected by chromatography on aluminium oxide (8 g.) and elution with pentane and benzene–pentane (1 : 4).

Cholest-5-en-4α-ol (XII; R = H).—(*a*) 4α-Acetoxycholest-5-ene (150 mg.) was hydrolysed by treatment with lithium aluminium hydride in ether to give, after the usual working up, cholest-5-en-4α-ol (120 mg.), m. p. 144—145°, $[\alpha]_D$ −50° (*c*, 0·55), after recrystallisation from acetone–pentane, identical with a specimen prepared by the method of Karrer, Sareen, Asmis, and Schwyzer (*loc. cit.*).

(*b*) Cholest-5-en-4-one (41 mg.) was treated with a solution of lithium aluminium hydride (60 mg.) in ether (20 c.c.) for 0·5 hr. The usual working up gave cholest-5-en-4α-ol (40 mg.), m. p. and mixed m. p. 144—145°, after crystallisation from acetone–pentane.

4α-Methoxycholest-5-ene (XIII). Cholest-5-en-4α-ol, by methylation in an atmosphere of nitrogen with potassium and methyl iodide in boiling benzene, gave 4α-methoxycholest-5-ene, m. p. 86° after crystallisation from ether–methanol (cf. Schmid and Kägi, *loc. cit.*).

Cholestan-4α-ol (XIV).—Cholest-5-en-4α-ol (50 mg.) was hydrogenated with platinum oxide (25 mg.) in ethyl acetate (5 c.c.) containing acetic acid (5 c.c.) to give, after the usual working up, cholestan-4α-ol, m. p. 188—189°, after recrystallisation from acetone.

5-Hydroxycholestan-4-one (X).—Cholestane-4β : 5-diol (3 g.), dissolved in a mixture of ether

(65 c.c.), methanol (12 c.c.), and water (11 c.c.), was treated with *N*-bromosuccinimide (2 g.); after 40 min. ether was added, and the solution washed with water, sodium metabisulphite solution, and water, dried, and evaporated. The solid residue (2·9 g.) by recrystallisation from methanol gave the *ketol*, m. p. 159°, $[\alpha]_D$ +55° (*c*, 1·4) [Found (after drying at 100°/0·01 mm. for 3 hr.): C, 80·8; H, 11·1. $C_{27}H_{46}O_2$ requires C, 80·55; H, 11·5%].

Reduction of 5-Hydroxycholestan-4-one (X) *with Lithium Aluminium Hydride.*—The ketol (25 mg.) was reduced with lithium aluminium hydride (50 mg.) in ether at 15°. Working up gave a solid (25 mg.), which by recrystallisation from ether–pentane yielded cholestane-4β : 5-diol, m. p. and mixed m. p. 172°.

Reduction of 5-Hydroxycholestan-4-one (X) *with Sodium and Propanol.*—Sodium (7 g.) was added gradually to a solution of the ketol (1·4 g.) in boiling propan-1-ol (100 c.c.); after refluxing for 3 hr., the solution was poured into water, propanol largely removed in a vacuum, and a solid (1·34 g.) isolated in the usual manner. Crystallisation from acetone–methanol (1 : 5) gave cholestan-4α-ol (390 mg.), m. p. 188°, $[\alpha]_D$ +6° (*c*, 0·8), characterised by preparation, with acetic anhydride in pyridine at 20°, of the *acetate*, m. p. 110°, $[\alpha]_D$ +14·5° (*c*, 1·0), after crystallisation from acetone [Found (after drying at 65°/0·01 mm. for 3 hr.): C, 80·85; H, 11·45. $C_{29}H_{50}O_2$ requires C, 80·85; H, 11·6%]. The material from the acetone–methanol mother-liquor failed to crystallise and was chromatographed on aluminium oxide (50 g.); elution with benzene gave cholestan-4α-ol (400 mg.), m. p. 188°, whilst use of ether–benzene (1 : 9) gave cholestane-4α : 5-diol (376 mg.), m. p. 133—135°, identical with the preparation described above.

Cholestan-4-one (XV).—Cholestan-4α-ol (150 mg.) was dissolved in acetic acid (10 c.c.) and oxidised with chromium trioxide (300 mg.) in 90% acetic acid (3 c.c.). After 48 hr. at 20°, the solution was evaporated at 30—35°/10 mm., and the product isolated in the usual way, to yield cholestan-4-one, m. p. 96°, $[\alpha]_D$ +27° (*c*, 0·6), after crystallisation from methanol; Barton and Rosenfelder (*J.*, 1951, 1032) record m. p. 94—96°.

Reduction of Cholestan-4-one with Lithium Aluminium Hydride.—Cholestan-4-one (308 mg.) was treated with lithium aluminium hydride (107 mg.) in ether at 15° for 1 hr. The product, an oil, was chromatographed on aluminium oxide (9 g.) in pentane; elution with pentane yielded cholestan-4-one (9 mg.), m. p. and mixed m. p. 96°, and elution with benzene gave cholestan-4β-ol (265 mg.), m. p. 135°, $[\alpha]_D$ +31° (*c*, 0·9), after crystallisation from methanol, whilst elution with ether–benzene (1 : 4) furnished cholestan-4α-ol (22 mg.), m. p. 188—190°, after recrystallisation from acetone.

Cholest-5-en-4-one (XVI).—5-Hydroxycholestan-4-one (150 mg.), dissolved in pyridine (5 c.c.), was treated with thionyl chloride (0·5 c.c.) at 0°; after 0·5 hr., at 20°, the solution was poured into water and worked up in the usual way. The product (110 mg.) was purified by chromatography on aluminium oxide (3 g.); elution with pentane gave cholest-5-en-4-one, m. p. 111°, $[\alpha]_D$ −34° (*c*, 0·54), $\lambda_{max.}$ 242 mμ (log ε 3·85), after recrystallisation from acetone, giving a yellow colour with tetranitromethane–chloroform. Butenandt and Ruhenstroth-Bauer (*loc. cit.*) give m. p. 111—112°, $[\alpha]_D$ −32°, $\lambda_{max.}$ 241 mμ (log ε 3·86).

Cholestane-5 : 6β-diol (XIX).—Cholest-5-ene was hydroxylated with performic acid according to the directions of Reich, Walker, and Collins (*loc. cit.*), to give, after chromatographic purification and crystallisation from aqueous ethanol, cholestane-5 : 6β-diol, double m. p. 60° and 125°, $[\alpha]_D$ −3° (*c*, 0·9); the 6β-monoacetate, prepared by acetic anhydride in pyridine at 20°, had m. p. 112—114°. Cholestane-5 : 6β-diol (120 mg.) was refluxed with acetyl chloride (2 c.c.) and dimethylaniline (2 c.c.) in purified chloroform (20 c.c.) for 4 hr.; the usual working-up gave an oil (122 mg.), which was purified by elution from aluminium oxide with pentane, to give 5 : 6β-*diacetoxycholestane*, m. p. 76°, $[\alpha]_D$ −33° (*c*, 0·9), after crystallisation from acetone [Found (after drying at 60°/0·01 mm. for 3 hr.): C, 76·3; H, 10·7. $C_{31}H_{52}O_4$ requires C, 76·2; H, 10·7%].

6β-*Acetoxycholest-4-ene* (XX; R = Ac).—6β-Acetoxycholestan-5-ol (1 g.) was dissolved in pyridine (15 c.c.) and treated with thionyl chloride (2 c.c.) at 0°; the mixture was kept at 20° for 0·5 hr., poured into water, and worked up in the usual way. The resultant oil (900 mg.) by elution from aluminium oxide with pentane afforded 6β-*acetoxycholest-5-ene*, m. p. 76—77°, $[\alpha]_D$ +74° (*c*, 0·9), after recrystallisation from methanol [Found (after drying at 60°/0·01 mm. for 2 hr.): C, 81·5; H, 11·2. $C_{29}H_{48}O_2$ requires C, 81·3; H, 11·3%], giving a yellow colour with tetranitromethane–chloroform. The acetate (20 mg.) was unchanged (m. p. and mixed m. p. 75—76°) by treatment with dry hydrogen chloride in chloroform (25 c.c.) containing ethanol (0·2 c.c.) at −5° for 1 hr.

Cholest-4-en-6α-ol (XX; R = H).—6β-Acetoxycholest-4-ene (700 mg.) was hydrolysed by treatment with lithium aluminium hydride in ether; working up in the usual way furnished an

oil, which crystallised from acetone, to give *cholest-4-en-6β-ol*, m. p. 86—87°, $[\alpha]_D$ +62° (*c*, 0·9) [Found (after drying at 60°/0·01 mm. for 2 hr.) : C, 83·2; H, 11·7. $C_{27}H_{46}O$ requires C, 83·8; H, 11·9%], giving a yellow colour with tetranitromethane–chloroform.

6β-*Methoxycholest-4-ene* (XXI).—Cholest-4-en-6β-ol (216 mg.) was heated in an atmosphere of nitrogen with " molecular " potassium (~200 mg.) in benzene for 1 hr., and then with methyl iodide (5 c.c.) for 3 hr. The product obtained by working up was purified by elution from aluminium oxide with pentane, to yield 6β-methoxycholest-4-ene, m. p. 97—98°, $[\alpha]_D$ +83° (*c*, 0·7) [Found (after drying at 60°/0·01 mm. for 2 hr.) : C, 83·5; H, 11·8. $C_{28}H_{48}O$ requires C, 83·9; H, 12·0%], giving a yellow colour with tetranitromethane in chloroform, and identical with the material isolated by Evans and Shoppee (*loc. cit.*).

6β-*Methoxycoprostane* (XXV).—6β-Methoxycholest-4-ene (77 mg.), dissolved in ethyl acetate (10 c.c.) containing acetic acid (2 c.c.), was shaken with platinum oxide (62 mg.) in hydrogen for 1 hr.; after working up and removal of traces of solvents and moisture by repeated evaporation with benzene in a vacuum, the residual oil (75 mg.) failed to crystallise. Chromatography on a long column of aluminium oxide (5 g.; activated at 250—310° for 1 hr.) prepared in pentane, and elution with pentane (2 × 5 c.c.) gave cholestane (7 mg.), m. p. and mixed m. p. 78—79°; further elution with pentane (6 × 5 c.c.) gave 6β-*methoxycoprostane* (67 mg.), m. p. 64—65°, $[\alpha]_D$ +9°, +11° (*c*, 0·4, 0·6), after recrystallisation from acetone [Found (after drying at 20°/0·01 mm. for 3 hr.) : C, 83·6; H, 12·6. $C_{28}H_{52}O$ requires C, 83·5; H, 12·5%].

6β-*Methoxycholestane*.—Cholestan-6β-ol (106 mg.), prepared by the method of Shoppee and Summers (*J.*, 1952, 3361), was methylated with potassium and methyl iodide in boiling benzene. The product, purified by elution from aluminium oxide with benzene–pentane (1 : 9), yielded 6β-methoxycholestane (40 mg.), double m. p. 52° and 77°, $[\alpha]_D$ +14° (*c*, 1·7) after recrystallisation from acetone [Found (after drying at 20°/0·01 mm. for 4 hr.) : C, 83·3; H, 12·2%].

Coprostan-6β-ol (XXIV; R = H).—(*a*) Cholest-4-en-6β-ol (750 mg.) was hydrogenated with platinum oxide (100 mg.) in ethyl acetate (20 c.c.) containing <1% of 60% perchloric acid. The product was purified by chromatography on aluminium oxide (22 g.) prepared in pentane; repeated elution with pentane gave cholestane (300 mg.), m. p. and mixed m. p. 80°, after recrystallisation from acetone. Elution with ether–benzene (1 : 4; 6 × 50 c.c.) gave *coprostan-6β-ol* (375 mg.), $[\alpha]_D$ +21° (*c*, 1·1) [Found (after distillation at 130°/0·01 mm.) : C, 83·3; H, 12·35. $C_{27}H_{48}O$ requires C, 83·4; H, 12·45%], which did not crystallise. The *acetate*, prepared by use of acetic anhydride in pyridine at 20°, crystallised readily from acetone–methanol in plates, m. p. 109—111°, $[\alpha]_D$ +22° (*c*, 0·55) [Found (after drying at 70°/0·01 mm. for 4 hr.) : C, 80·5; H, 11·85. $C_{29}H_{50}O_2$ requires C, 80·85; H, 11·7%], and exhibited infrared absorption bands at 1730 and 1242 $cm.^{-1}$. The acetate was also obtained by hydrogenation of 6β-acetoxycholest-4-ene (170 mg.) in ethyl acetate (15 c.c.) containing 60% perchloric acid (3 drops) with platinum oxide (101 mg.); the resultant oil (171 mg.) by chromatography on aluminium oxide and elution with pentane gave cholestane (30 mg.), m. p. and mixed m. p. 77—78°, whilst use of benzene–pentane (1 : 9) gave a solid (135 mg.) which by crystallisation from methanol gave coprostan-6β-yl acetate, m. p. and mixed m. p. 108—110°.

(*b*) Coprostane-3β : 6β-diol, prepared following Prelog and Tagmann's directions (*loc. cit.*), was converted into the diacetate, m. p. 137—139°, $[\alpha]_D$ +13°. The diacetate (2 g.) was refluxed with potassium hydroxide (5 g.) in methanol (750 c.c.) for 2 hr.; the solution was cooled, acidified to Congo-red with concentrated hydrochloric acid, neutralised with aqueous ammonia, concentrated in a vacuum, and allowed to cool. The concentrate was diluted with water and extracted with ether, and the ethereal extract dried and evaporated. The product was dissolved in benzene (40 c.c.), pentane (360 c.c.) added, and the solution set aside for 30 min.; coprostane-3β : 6β-diol (530 mg.), m. p. and mixed m. p. 198—200°, was removed by filtration, and the filtrate chromatographed on a column of aluminium oxide (60 g.) prepared in pentane. Elution with chloroform gave 6β-*acetoxycoprostan-3β-ol* (1·13 g.), m. p. 144°, $[\alpha]_D$ +11° (*c*, 0·9), after recrystallisation from acetone [Found (after drying at 55°/0·01 mm. for 6 hr.) : C, 78·0; H, 11·3. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%], whilst elution with methanol yielded coprostane-3β : 6β-diol (200 mg.), m. p. and mixed m. p. 198—200° after recrystallisation from ethyl acetate. 6β-Acetoxycoprostan-3β-ol (1 g.), dissolved in acetic acid (75 c.c.), was treated with chromium trioxide (200 mg.) in 96% acetic acid (25 c.c.) for 16 hr. at 20°. After evaporation at 30—35°/10 mm., the usual working-up gave an oil (972 mg.) which crystallised and then had m. p. 104—109°; purification by elution from aluminium oxide (30 g.) with benzene–pentane mixtures and recrystallisation from ethanol afforded 6β-*acetoxycoprostan-3-one*, m. p. 113—115°, $[\alpha]_D$ +20° (*c*, 2·57) [Found (after drying at 90°/0·01 mm. for 6 hr.) : C, 78·5; H, 11·1.

$C_{29}H_{48}O_2$ required C, 78·3; H, 10·9%]. The acetate (300 mg.) was refluxed with hydrazine (1 c.c.) and potassium hydroxide (600 mg.) in ethanol (25 c.c.) for 30 min.; ethylene glycol (20 c.c.) was added, aqueous ethanol (28 c.c.) removed by distillation, and the temperature raised to 196°. After refluxing at 196° for 3 hr., the mixture was allowed to cool, poured into water, and worked up in the usual manner. The resultant brown oil (231 mg.) was chromatographed on neutralised aluminium oxide (8 g.) in pentane; elution with benzene gave a colourless oil (211 mg.). To remove any ketonic material, the oil was dissolved in ethanol–acetic acid (9 : 1; 25 c.c.) and refluxed with Girard's reagent T (200 mg.) for 0·5 hr.; the cooled mixture was poured into water and extracted with ether, and the ethereal extract washed with 2N-sodium carbonate, dried, and evaporated. The product was chromatographed on neutralised aluminium oxide (6 g.) in pentane; repeated elution with pentane gave an oil (18 mg.), which did not crystallise and was discarded, whilst elution with benzene–pentane gave coprostan-6β-ol (180 mg.) as a colourless oil, $[\alpha]_D$ +21°; this did not crystallise, but by acetylation as usual at 25° for 14 hr. gave coprostan-6β-yl acetate, m. p. 100—105°, which after recrystallisation from acetone–methanol had m. p. and mixed m. p. 109—111°, $[\alpha]_D$ +22·5°.

Coprostan-6-one (XXVIII).—Coprostan-6β-ol [420 mg.; preparation (*a*)] was dissolved in acetic acid (15 c.c.) and treated with a 2% solution of chromium trioxide in acetic acid (9 c.c.) at 20° for 18 hr. After evaporation at 30—35°/10 mm., and isolation in the usual way the product (390 mg.) crystallised rapidly, and by recrystallisation from acetone gave *coprostan-6-one*, m. p. 133°, $[\alpha]_D$ −44° (*c*, 1·05) [Found (after drying at 70°/0·01 mm. for 4 hr.): C, 84·0; H, 11·95. $C_{27}H_{46}O$ requires C, 84·0; H, 12·0%]. Similarly coprostan-6β-ol [52 mg.; preparation (*b*)] by oxidation gave a product (50 mg.), m. p. 125—130°, which, thrice recrystallised from acetone, furnished coprostan-6-one, m. p. and mixed m. p. 133°. The ketone by reduction with lithium aluminium hydride in ether gave a non-crystalline product, which by acetylation as usual at 20° for 16 hr. gave coprostan-6β-yl acetate, m. p. and mixed m. p. 109—111°.

Coprostan-6-one (20 mg.) was refluxed with 1·5% methanolic potassium hydroxide (5 c.c.) for 0·5 hr.; after saturation with carbon dioxide, evaporation in a vacuum, and addition of water, the product was extracted with ether. The resultant oil (20 mg.) crystallised and by recrystallisation from acetone yielded cholestan-6-one, m. p. and mixed m. p. 95—96°, $[\alpha]_D$ −2°. Coprostan-6-one (20 mg.) was refluxed with acetic acid (1 c.c.) containing concentrated hydrochloric acid (1 drop) for 0·5 hr.; the mixture was diluted with water and extracted with ether. The ethereal extract was washed with water and with 2N-sodium carbonate, dried, and evaporated, to give cholestan-6-one, m. p. and mixed m. p. 95—96°. Coprostan-6-one (20 mg.), dissolved in moist benzene (5 c.c.), was introduced on a column of aluminium oxide (1 g.) prepared in pentane; after 16 hr. elution with benzene gave cholestan-6-one, m. p. and mixed m. p. 95—96°.

Reaction of Coprostan-6β-ol with Thionyl Chloride: 6ξ-Chlorocoprostane (XXVII).—Coprostan-6β-ol (100 mg.), dissolved in pyridine (10 c.c.), was treated with thionyl chloride (0·5 c.c.) at 0°, and the mixture set aside at 20° for 0·5 hr. The usual working-up gave an oil (82 mg.), which was purified by filtration of a pentane solution through a column of aluminium oxide; the product on crystallisation from acetone gave *6ξ-chlorocoprostane*, m. p. 85°, $[\alpha]_D$ −59° (*c*, 1·2) [Found (after drying at 50°/0·01 mm. for 3 hr.): C, 79·45; H, 11·4. $C_{27}H_{47}Cl$ requires C, 79·65; H, 11·6%].

Reduction of 6ξ-Chlorocoprostane with Sodium and Pentyl Alcohol.—6ξ-Chlorocoprostane (80 mg.) was dissolved in pentyl alcohol (25 c.c.), and sodium (1 g.) gradually added to the refluxing solution. After 3 hr., the solution was worked up in the usual way, yielding coprostane, m. p. and mixed m. p. 70—71°.

Cholestane-5 : 6α-diol (XXXII).—Cholest-5-ene (1·03 g.), in ether (50 c.c.) was treated with osmium tetroxide (1 g.) in ether (10 c.c.) containing pyridine (2 c.c.); after 63 hr. at 20°, ether was removed by evaporation and the product refluxed with aqueous-ethanolic sodium sulphite for 3 hr. The solution was then filtered through charcoal, evaporated to dryness in a vacuum, and shaken with ether and 3N-sodium hydroxide containing mannitol; the ethereal layer was separated, washed with water, dried, and evaporated, to give *cholestane-5 : 6α-diol* (950 mg.), m. p. 180—181°, $[\alpha]_D$ +15° (*c*, 1·0), after recrystallisation from acetone [Found (after drying at 100°/0·01 mm. for 2 hr.): C, 80·1; H, 11·85. $C_{27}H_{48}O_2$ requires C, 80·1; H, 11·95%]. The *6α-monoacetate*, prepared as usual at 20° and purified by filtration of a benzene–pentane solution through a layer of aluminium oxide, had m. p. 117—118°, $[\alpha]_D$ +24° (*c*, 1·0), after recrystallisation from acetone–methanol [Found (after sublimation at 120°/0·01 mm.): C, 78·0; H, 11·2. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%]. The 5 : 6α-diol with refluxing acetyl chloride and dimethylaniline in purified chloroform gave 5 : 6α-diacetoxycholestane as an oil, $[\alpha]_D$

+43° (*c*, 0·9), which did not crystallise, although hydrolysis with lithium aluminium hydride in ether regenerated the 5 : 6α-diol, m. p. and mixed m. p. 180—181°.

6α-Acetoxycholest-4-ene (XXXIII; R = Ac).—6α-Acetoxycholestan-5-ol (420 mg.) in pyridine (5 c.c.) was treated with thionyl chloride (1·0 c.c.) at 0°; after 0·5 hr. at 20°, the product was isolated in the usual way and purified by chromatography on aluminium oxide. Elution with pentane gave *6α-acetoxycholest-4-ene*, m. p. 95—98°, $[\alpha]_D$ +78·5° (*c*, 0·5), after crystallisation from acetone [Found (after drying at 60°/0·01 mm. for 3 hr.): C, 80·95; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%], giving a yellow colour with tetranitromethane in chloroform. In a second run, 6α-acetoxycholestan-5-ol (346 mg.) on treatment with thionyl chloride (1·3 c.c.) in pyridine (5 c.c.) at 0°, gave 6α-acetoxycholest-4-ene (310 mg.), m. p. 95—98°, after recrystallisation from methanol.

Cholest-4-en-6α-ol (XXXIII; R = H).—(*a*) 6α-Acetoxycholest-4-ene (410 mg.) was refluxed with 5% methanolic potassium hydroxide (25 c.c.) for 1 hr.; after saturation with carbon dioxide and evaporation in a vacuum, the usual procedure gave *cholest-4-en-6α-ol* (390 mg.), m. p. 139—140°, $[\alpha]_D$ +64° (*c*, 0·55), after recrystallisation from acetone [Found (after drying at 100°/0·01 mm. for 2 hr.): C, 83·55; H, 11·8. $C_{27}H_{46}O$ requires C, 83·8; H, 12·0%], giving a yellow colour with tetranitromethane–chloroform.

(*b*) 6α-Acetoxycholest-4-ene (230 mg.) in ether (25 c.c.) was treated with excess of lithium aluminium hydride at 36° for 2 hr. The usual working up afforded a solid, m. p. 136—140°, which by recystallisation from acetone–methanol yielded cholest-4-en-6α-ol, m. p. 140—143°, mixed m. p. 140—142°.

(*c*) Cholest-4-en-6-one (XXXI) (121 mg.) in ether (25 c.c.) was treated with excess of lithium aluminium hydride at 36° for 30 min. The usual processing furnished a solid (118 mg.), m. p. 115—125°. Elution from aluminium oxide (6 g.) with benzene gave a little oil (discarded), whereafter elution with ether gave cholest-4-en-6α-ol (92 mg.), m. p. and mixed m. p. 140—141°. In a second experiment, cholest-4-en-6-one (120 mg.) was treated with lithium aluminium hydride in ether (20 c.c.) for 15 min. at 36°. The product, isolated in the usual way, by crystallisation from acetone–methanol gave cholest-4-en-6α-ol (110 mg.), m. p. 139—142°, mixed m. p. 140—141°.

6α-Methoxycholest-4-ene (XXXIV).—Cholest-5-en-6α-ol (64 mg.) by methylation in an atmosphere of nitrogen with potassium and methyl iodide in boiling benzene gave only cholesta-3 : 5-diene (40 mg.), m. p. and mixed m. p. 76—78° after crystallisation from acetone. The stenol (175 mg.) was converted into the potassium derivative by vigorous agitation with "molecular" potassium in benzene at 30—35°; methyl iodide (5 c.c.) was added and shaking continued at 35° for 3 hr. The usual working-up gave a product, which by chromatography on aluminium oxide (5 g.) and elution with pentane yielded an oil (65 mg.), which failed to crystallise on inoculation with cholesta-3 : 5-diene. The oil was rechromatographed on a long column of aluminium oxide (activated at 250—310° for 1 hr.) prepared in pentane; elution with pentane (4 × 100 c.c.) furnished cholesta-3 : 5-diene (29 mg.), m. p. and mixed m. p. 79—80°, after crystallisation from acetone, but elution with benzene–pentane (1 : 9; 3 × 10 c.c.) gave 6α-methoxycholest-4-ene (35 mg.), $[\alpha]_D$ +20° (*c*, 1·16), which did not cystallise and at 70° decomposed to give cholesta-3 : 5-diene.

Coprostan-6α-ol (XXX; R = H).—(*a*) Cholest-4-en-6α-ol (225 mg.) was hydrogenated with platinum oxide (55 mg.) in ethyl acetate (21 c.c.) containing 60% perchloric acid (1 drop). The theoretical amount of hydrogen was absorbed in 15 min. and the product purified by chromatography on a column of aluminium oxide (5 g.) prepared in pentane; elution with pentane gave cholestane (15 mg.), m. p. and mixed m. p. 79°, after crystallisation from acetone. Elution with ether–benzene (1 : 9) gave coprostan-6α-ol, $[\alpha]_D$ +18° (*c*, 0·7), which did not crystallise, whilst the acetate, $[\alpha]_D$ +23° (*c*, 1·57), prepared as usual at 20°, also failed to crystallise after chromatography on aluminium oxide, elution with pentane, and distillation in a high vacuum.

(*b*) 6α-Acetoxycholest-4-ene (68 mg.) was hydrogenated with platinum oxide (48 mg.) in ethyl acetate (10 c.c.) containing acetic acid (5 c.c.) for 1 hr. The usual working-up gave an oil (67 mg.) which was chromatographed on chromium oxide (2 g.) prepared in pentane. Elution with pentane yielded cholestane (9 mg.), m. p. and mixed m. p. 78° after crystallisation from acetone, whilst elution with benzene–pentane (1 : 9) gave 6α-acetoxycoprostane (XXX; R = Ac) (56 mg.) as an oil, $[\alpha]_D$ +23° (*c*, 1·0), hydrolysed by methanolic potassium hydroxide to coprostan-6α-ol, an oil, $[\alpha]_D$ +18° (*c*, 0·7).

Coprostan-6α-ol (130 mg.) in acetic acid (2 c.c.) was oxidised with chromium trioxide (50 mg.) in 98% acetic acid (2 c.c.) at 20° to coprostan-6-one, m. p. and mixed m. p. 132—134° after two recrystallisations from acetone.

Reaction of Coprostan-6α-ol (XXX; R = H) *with Thionyl Chloride.*—Coprostan-6α-ol (150 mg.) in pyridine (10 c.c.) was treated with thionyl chloride (0·75 c.c.) at 0°; the mixture, after 0·5 hr. at 20°, was worked up in the usual way. The resultant oil was chromatographed on aluminium oxide (6 g.) in pentane; elution with pentane (2 × 5 c.c.) gave cholest-5-ene (37 mg.), m. p. and mixed m. p. 94—95°, after crystallisation from acetone. Further elution with pentane yielded a viscous oil (105 mg.), which gave no colour with tetranitromethane in chloroform, contained sulphur, and probably consisted of coprostan-6α-yl sulphite.

5-Hydroxycholestan-6-one (XXXVI).—Prepared from cholestane-5 : 6β-diol by oxidation with *N*-bromosuccinimide, the ketol had m. p. 153° (cf. Reich, Walker, and Collins, *loc. cit.*).

Dehydration.—This material (1·07 g.) was treated in pyridine (20 c.c.) with thionyl chloride (4 c.c.) at 0°; the solution at once became deep-red, and after 0·5 hr. at 20° was poured into ice and 3N-hydrochloric acid. The product, isolated in the usual way and purified by elution from aluminium oxide (100 g.) with pentane, gave cholest-4-en-6-one (450 mg.), m. p. 106—108° after recrystallisation from acetone–methanol, giving a yellow colour with tetranitromethane–chloroform.

Reduction of 5-Hydroxycholestan-6-one (XXXVI).—(*a*) *With lithium aluminium hydride.* The ketol (30 mg.) was treated with lithium aluminium hydride in ether (5 c.c.) at 36° for 0·5 hr.; the product, isolated in the usual way and crystallised from aqueous acetone, gave cholestane-5 : 6β-diol, m. p. and mixed m. p. 123—125°.

(*b*) *With sodium and propan-1-ol.* The ketol (1·1 g.) in boiling propanol (90 c.c.) was treated gradually with sodium (7 g.), and the solution refluxed for 4 hr. The usual working-up gave an oil (1·05 g.), which was chromatographed on aluminium oxide (35 g.) prepared in pentane. Elution with benzene–pentane (1 : 1; 5 × 100 c.c.) yielded cholestan-6α-ol (283 mg.), m. p. 130°, $[\alpha]_D$ +37° (*c*, 0·5), after recrystallisation from acetone; it was characterised as the acetate, m. p. 78—79°, $[\alpha]_D$ +74° (*c*, 0·6). Elution with ether–benzene (1 : 1; 4 × 100 c.c.) gave cholestane-5 : 6α-diol, m. p. and mixed m. p. 180—181°, after recrystallisation from acetone; this was characterised as the 6α-monoacetate, m. p. and mixed m. p. 117—118° (from acetone–methanol). Finally, elution with ether afforded *coprostane-5 : 6α-diol*, m. p. 141—142°, $[\alpha]_D$ +31° (*c*, 0·8), after recrystallisation from acetone [Found (after drying at 100°/0·01 mm. for 2 hr.): C, 80·1; H, 12·1. $C_{27}H_{48}O_2$ requires C, 80·1; H, 11·95%]; acetylation as usual at 20° gave 6α-acetoxycoprostan-5-ol, $[\alpha]_D$ +33° (*c*, 0·9) after chromatographic purification, which did not crystallise.

5-Hydroxycoprostan-6-one (XXXVIII).—Coprostane-5 : 6α-diol (35 mg.) in acetic acid (6 c.c.) was treated with chromium trioxide (20 mg.) in 98% acetic acid (1·0 c.c.) at 20° for 12 hr. The usual working-up afforded an oil, which crystallised on trituration with acetone and on recrystallisation from acetone gave *5-hydroxycoprostan-6-one*, m. p. 102—103°, $[\alpha]_D$ −18° (*c*, 0·6) [Found (after drying at 70°/0·01 mm. for 3 hr.): C, 78·5; H, 11·35. $C_{27}H_{46}O_2.\frac{1}{2}H_2O$ requires C, 78·75; H, 11·5%]. The ketol, on reduction with lithium aluminium hydride in ether, regenerated coprostane-5 : 6α-diol, m. p. and mixed m. p. 139—141°.

Dehydration of 6α-Acetoxycoprostan-5-ol to 6α-Acetoxycholest-4-ene (XXXIII; R = Ac).—6α-Acetoxycoprostan-5-ol (57 mg.), dissolved in pyridine (1 c.c.), was treated with thionyl chloride (0·25 c.c.) at 0°; after 0·5 hr. at 20°, the mixture was worked up in the usual manner. The product was chromatographed on a column of aluminium oxide (1·5 g.) prepared in pentane; elution with pentane gave 6α-acetoxycholest-4-ene, m. p. and mixed m. p. 92—93°.

Attempted Epimerisation of Cholestane-5 : 6α-diol (XXXII) *and Cholestan-5-ol.*—(*a*) The 5α : 6α-diol (67 mg.) was dissolved in boiling propan-1-ol (50 c.c.), and sodium (5 g.) was gradually added; after 4 hours' refluxing, working up gave cholestane-5 : 6α-diol (65 mg.), m. p. and mixed m. p. 175—176°.

(*b*) Cholestan-5-ol (83 mg.), prepared by the method of Plattner, Petrzilka, and Lang (*Helv. Chim. Acta*, 1944, **27**, 513), was dissolved in boiling propanol, and sodium (5 g.) was gradually added; after 4 hours' refluxing, working-up afforded cholestan-5-ol (78 mg.), m. p. and mixed m. p. 97—99°.

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Pavine. Part I. The Structure and Chemistry of Pavine.

By Alan R. Battersby and R. Binks.

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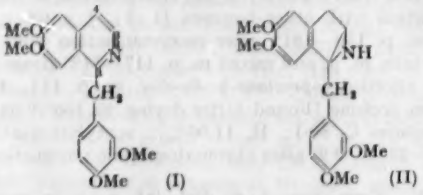
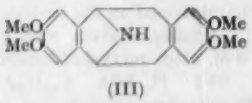
Pavine has been shown to possess the structure (IX) by degradation to 2 : 2′-dicarboxy-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (XV). The latter is obtained from pavine by two applications of Hofmann's degradation, with hydrogenation after the first, and oxidation of the final neutral product. Both stages of the Hofmann degradation have been found to proceed without rearrangement. In addition to several new derivatives of 2′ : 3′ : 2″ : 3″-tetramethoxy-1 : 2-5 : 6-dibenzo*cyclo*octa-diene and -triene, the corresponding tetraene has been prepared. A number of reactions of pavine derivatives have been explained and the mechanism of formation of pavine is discussed.

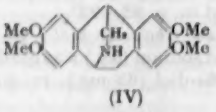
Reduction of papaverine (I), $C_{20}H_{21}O_4N$, with tin and hydrochloric acid affords 1 : 2 : 3 : 4-tetrahydropapaverine and a crystalline base, originally named "tetrahydropapaverine" (Goldschmiedt, *Monatsh.*, 1886, **7**, 485; 1898, **19**, 324), but renamed pavine by Pyman and Reynolds (*J.*, 1910, **97**, 1320) after its molecular formula had been shown to be $C_{20}H_{23}O_4N$ (Pyman, *J.*, 1909, **95**, 1610). Pavine is a secondary base, resistant to attempted reduction or mild oxidation, but susceptible to degradation by Hofmann's





(III)

method. One application of this degradation afforded *N*-methylpavinemethine which retains the nitrogen atom of pavine. These properties, taken with the existence of optically active forms of pavine (Pope and Peachey, *J.*, 1898, **73**, 893), led Pyman (*J.*, 1915, **107**, 176) to propose the structure (II) for the base. Schöpf in a brief communication (*Experientia*, 1949, **5**, 201) rejected this formula on the grounds that the ethyleneimine ring would be opened by acid whereas *N*-methylpavine is recovered unchanged after demethylation with hydriodic acid followed by remethylation. As a result of his further finding that 1 : 2-dihydro-*N*-methylpapaverine yields *N*-methylpavine under acidic



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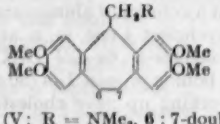
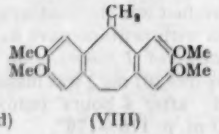


(V; R = NMe_2, 6 : 7-double bond)
(VI; R = NMe_3)
(VII; R = NMe_3^+}I^-)

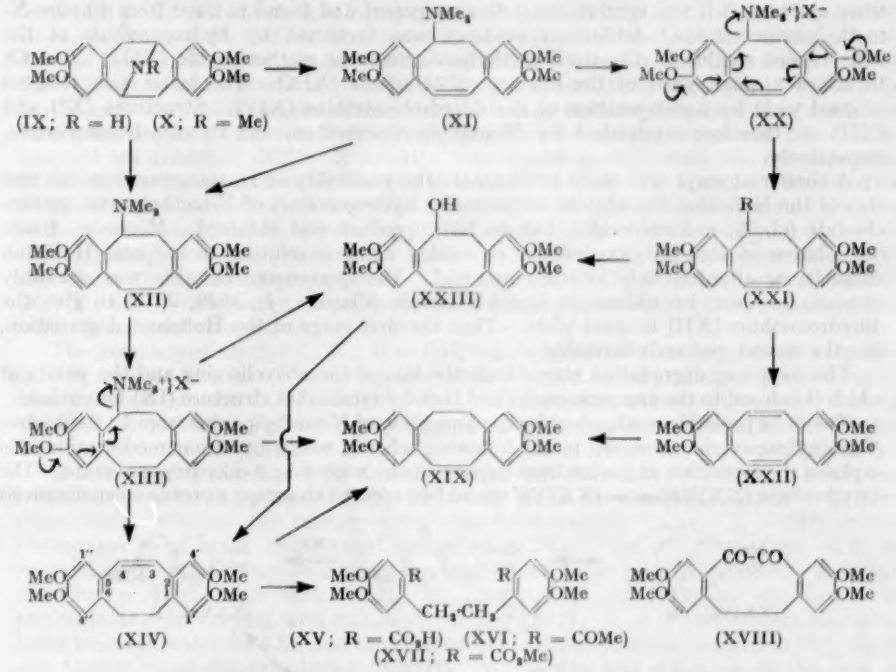


(VIII)

conditions, Schöpf suggested structures (IV) and (IX) for pavine, but left the choice undecided; these structures will be used below as the basis for discussion. A third structure (III) which is consistent with much of the chemistry of pavine can only be derived from papaverine by deep-seated changes; it need not be considered further, however, since it represents an internally compensated molecule.

The pavine used in our work was prepared from papaverine by Pyman's chemical reduction method (*J.*, 1909, **95**, 1610), and *N*-methylpavine was obtained by cyclisation of 1 : 2-dihydro-*N*-methylpapaverine essentially as outlined by Schöpf (*loc. cit.*). Since no experimental directions have been published for the latter route, details of the two

procedures we used are given in the Experimental section. One, which involved long heating of a solution of 1 : 2-dihydro-*N*-methylpapaverine in constant-boiling hydrochloric acid, gave a phenolic product. This was methylated with an excess of dimethyl sulphate, and *N*-methylpavine was isolated as its crystalline methosulphate in 89% yield. The second method employed a mixture of formic and phosphoric acid (cf. Braude and Forbes, *J.*, 1953, 2208) and afforded 72% of *N*-methylpavine directly. Methylation of pavine from Pyman's route with formic acid and formaldehyde gave *N*-methylpavine, identical with that from the other route.



Pyman (*J.*, 1915, **107**, 176) studied the oxidation of *N*-methylpavinemethine under mild conditions and isolated a dicarboxylic acid which is formed without loss of carbon. The methine therefore possesses the grouping –CH=CH– in a ring and can be represented by (V) or (XI). As briefly reported earlier (*Chem. and Ind.*, 1954, 1455), we find that the methine is reduced catalytically with the uptake of one mol. of hydrogen to yield a crystalline base, dihydro-*N*-methylpavinemethine (VI) or (XII). Methyl iodide in ethereal solution at room temperature converted the dihydromethine into its methiodide (VII) or (XIII; X = I) which was degraded by a second application of Hofmann's method. Dihydropavinebismethine (VIII) or (XIV) was formed together with trimethylamine and a little regenerated dihydro-*N*-methylpavinemethine. A decision between the structures (VIII) and (XIV) for the nitrogen-free product was sought by oxidation of the ethylenic link with potassium permanganate. The main product was a crystalline dibasic acid, $C_{20}H_{22}O_8$, isolated in 60% yield, a result in accord with the structure (XIV); the dicarboxylic acid would thus be expected to have the structure (XV). Proof was obtained by synthesis of 2 : 2′-dicarboxy-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (XV) from the related ketone (XVI) (following paper) by the haloform reaction. The synthetic acid and that from the oxidation of (XIV) were identical, as were their dimethyl esters (XVII).

A minor product from the oxidation of the dihydrobismethine (XIV) was a neutral

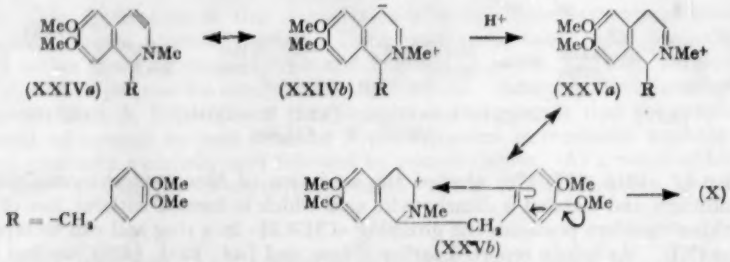
carbonyl compound, $C_{20}H_{20}O_6$, which gave a negative reaction in the *o*-dianisidine test for aldehydes (Feigl, " Qualitative Analysis by Spot Tests," Elsevier, New York, 3rd English Edn., p. 340). Though the small amount of material available precluded rigorous identification, the most probable structure for this product is (XVIII); a micro-test with *o*-phenylenediamine for the α-diketone residue was inconclusive.

Structure (XIV) having been proved for dihydropavinebismethine, structure (XII) follows for dihydro-*N*-methylpavinemethine in the absence of any rearrangement. There is, however, the somewhat unlikely possibility that the latter base is in fact (VI) which undergoes ring expansion during exhaustive methylation. This possibility was discounted when the base (VI) was synthesised (following paper) and found to differ from dihydro-*N*-methylpavinemethine. Additional evidence was furnished by hydrogenolysis of the benzylamine residue in dihydro-*N*-methylpavinemethine methochloride (XIII; X = Cl) to afford a small yield of the dibenz*ocyclo*octadiene (XIX). The latter also resulted in good yield by hydrogenation of the dihydrobismethine (XIV). Structures (XI) and (XII) are therefore established for *N*-methylpavinemethine and its dihydro-derivative, respectively.

A similar attempt was made to eliminate the possibility of rearrangement in the first step of the Hofmann degradation of pavine by hydrogenolysis of *N*-methylpavine methochloride (cf. X, methochloride), but no basic product was obtained. Moreover, Emde degradation of this salt, carried out in weakly alkaline solution to suppress Hofmann elimination, afforded only starting material. The quaternary chloride was smoothly cleaved, however, by sodium in liquid ammonia (Clayson, *J.*, 1949, 2016) to give the dihydromethine (XII) in good yield. Thus the first stage of the Hofmann degradation, like the second, proceeds normally.

The foregoing degradation shows both the size of the alicyclic ring and the points at which it is fused to the aromatic nuclei and thereby establishes structure (IX) for pavine.

The most probable mechanism for the formation of *N*-methylpavine from 1 : 2-dihydro-*N*-methylpapaverine is shown in the following scheme, which by minor modification also explains the formation of pavine from papaverine by way of 1 : 2-dihydropapaverine. The dihydro-base (XXIV*a*) ⟷ (XXIV*b*) would be expected to accept a proton when dissolved



in strong acid, to give (XXV*a*), a double-bond shift which has been shown to occur under acidic conditions for several αβ-unsaturated tertiary amines (Leonard and Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781). Since form (XXV*a*) is stabilised by resonance with the carbonium ion (XXV*b*), cyclisation should take place with the activated *p*-position of the aromatic nucleus to afford *N*-methylpavine. A similar mechanism has been proposed to explain the dimerisation of indole (Smith, *Chem. and Ind.*, 1954, 1451).

If the above scheme is correct, it is a corollary that salts of 1 : 2-dihydro*iso*quinolines should show cationoid reactivity at position 3. The further corollary that 1 : 2-dihydro-*iso*quinolines should have anionoid reactivity at position 4 is related to the known reaction where *C*-alkylation by alkyl halides occurs at the β-position of αβ-unsaturated tertiary amines (Hamilton and Robinson, *J.*, 1916, **109**, 1029; Robinson and Saxton, *J.*, 1952, 976; Stork, Terrell, and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1954, **76**, 2029). Both of these reactions offer interesting possibilities for syntheses in the *iso*quinoline series.

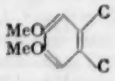
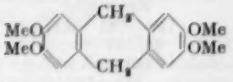
It is now possible to explain some of the reactions shown by certain derivatives of

pavine. Thus, *N*-methylpavinemethine methiodide (XX; X = I) is largely decomposed in aqueous solution after 15 min. at 100° to give an alcohol, $C_{20}H_{22}O_5$ (Pyman, *loc. cit.*). We have obtained the same product, rather than the expected dibenzo*cyclo*octatetraene (XXII), from attempted Hofmann degradation of the methohydroxide (XX; X = OH) in 50% aqueous potassium hydroxide. The alcohol was also formed by boiling an aqueous solution of the hydroxide (XX; X = OH); 83% had decomposed to the alcohol after 15 min. When Pyman's decomposition of the methiodide (XX; X = I) was repeated, it was found that the alcohol was contaminated with a second product, not fully characterised, but which contained iodine and was readily hydrolysed by aqueous alkali. Structure (XX) for *N*-methylpavinemethine metho-salts is in accord with all these results since quaternary salts derived from *p*-methoxybenzylamines are known to undergo ready thermal decomposition by a unimolecular mechanism (Battersby and Openshaw, *J.*, 1949, S 59; Norcross and Openshaw, *J.*, 1949, 1174; Pailer and Bilek, *Monatsh.*, 1948, **79**, 135). In the case of *N*-methylpavinemethine methiodide or methohydroxide, the intermediate carbonium ion combines with hydroxyl ion to afford the alcohol, which can therefore be assigned the structure (XXI; R = OH). The second product from the decomposition of the methiodide is presumably the benzyl iodide (XXI; R = I) arising by combination of the intermediate carbonium ion with an iodide ion. Support for the structure assigned to the alcohol was obtained by reducing it catalytically to its crystalline dihydro-derivative (XXIII) which was dehydrated under acidic conditions to the dihydrobismethine (XIV) identical with the earlier preparation. The sample of (XIV) prepared from the alcohol (XXIII) was hydrogenated smoothly to the dibenzo*cyclo*octadiene (XIX), also identical with the material obtained above.

The unsaturated alcohol (XXI; R = OH) was dehydrated when heated with sulphuric acid in aqueous dioxan. Chromatography then afforded the crystalline tetramethoxydibenzo*cyclo*octatetraene (XXII) in 11% yield. This product showed the normal lack of aromatic character and could be hydrogenated under mild conditions to the related dibenzo*cyclo*octadiene (XIX).

It is interesting that under the same Hofmann conditions (hot 50% aqueous potassium hydroxide), the methohydroxide (XX; X = OH) yields the alcohol (XXI; R = OH) by replacement, whereas the corresponding dihydro-derivative (XIII; X = OH) suffers elimination to give the unsaturated compound (XIV). This can be understood if, in contrast to the rapid heterolysis which has been shown to occur with (XX), only slow S_N1 substitution takes place with (XIII), so allowing the *E*2 Hofmann elimination to predominate. In keeping with this, only 36% of (XIII; X = I) had decomposed after being boiled in water for 4 hr. and the product of the decomposition, isolated in 32% yield, was the expected dihydro-alcohol (XXIII). We ascribe this difference in the ease of separation of a carbonium ion from (XX) and (XIII) to electromeric assistance in the former from two *p*-methoxy-aromatic residues as compared with one in the latter case.

On the above basis, the product, $C_{16}H_9(OMe)_5$, obtained by Pyman (*loc. cit.*) by the action of boiling methanol on (XX; X = I) is clearly the methyl ether (XXI; R = OMe), and his second product, $C_{20}H_{21}O_4Cl$, prepared by treating the alcohol (XXI; R = OH) with acetyl chloride, can be assigned the structure (XXI; R = Cl).

(XXVI)   (XXVII)

The ultraviolet absorption spectra recorded in Table 1 show that pavine and compounds (XII), (XIX), and (XXIII), which have no double bond in conjugation with the aromatic nuclei, have the normal absorption attributable to two isolated residues of the type (XXVI). The absorption of 9 : 10-dihydro-2 : 3 : 6 : 7-tetramethoxyanthracene (XXVII) (Robinson, *J.*, 1915, **107**, 267) was recorded for comparison. The compounds (XI), (XIV), and (XXI; R = OH), which possess a conjugated double bond, absorb more intensely and at somewhat longer wavelengths, but the shifts are only small. This is because the coplanar state of the aromatic nuclei and the double bond necessary for full

interaction cannot be achieved in molecules of type (XXI) which are shaped like a partly opened hinge.

[*Added June 30th, 1955.*]—Professor Schöpf has kindly informed us that he and his colleagues have also established structure (IX) for pavine [work in course of publication, summarised in a lecture (*Angew. Chem.*, 1950, **62**, 453) for which no abstract was available]. Further comment is reserved for a future communication.

TABLE 1. *Ultraviolet absorption maxima and minima* (mμ) *determined in ethanol.*

	Maxima	ε	Minima	ε
Pavine (IX)	225 *	16,520	251	612
	287·5	8,700		
Dihydro-*N*-methylpavinemethine (XII)	225 *	16,600	255	614
	286	6,050		
The dibenzo*cyclo*octadiene (XIX)	225 *	15,960	253	524
	285·5	7,020		
The alcohol (XXIII)	227 *	16,290	255·5	920
	285	6,380		
The 9 : 10-dihydroanthracene (XXVII)	233	22,850	223·5	19,620
	291·5	7,430	261	1,500
N-Methylpavinemethine (XI)	290·5	9,450	272	7,690
N-Methylpavinemethine HCl	290·5	9,540	270	7,870
Dihydropavinebismethine (XIV)	296	11,040	267·5	7,200
	345 *	2,420		
The alcohol (XXI; R = OH)	292·5	11,410	267	8,700
	345 *	900		
The dibenzo*cyclo*octatetraene (XXII)	296·5	9,180	277	7,160
Oxidation product (XVIII?)	238	28,800	222	17,300
	284·5	13,500	256	7,190
	322	11,400	303·5	10,130

* Inflexion.

EXPERIMENTAL

Analyses are by Mr. B. S. Noyes. Analytical samples were dried at 100° *in vacuo* over phosphoric oxide, unless otherwise stated.

N-Methylpavine (X).—(a) *From pavine.* Pavine (0·155 g.), prepared by Pyman's method (*J.*, 1909, **95**, 1610) and having m. p. 199—200° [Pyman (*loc. cit.*) records 201—202° (corr.)], was treated with formic acid (*d* 1·2; 2 ml.) and 37% aqueous formaldehyde (4 ml.). After being heated under reflux at 100—110° for 15 hr., the mixture was poured into 0·1N-hydrochloric acid (10 ml.) and extracted thrice with ether, and the ether extract shaken with 0·1N-hydrochloric acid (2 × 5 ml.). The combined aqueous layers were basified with an excess of sodium hydroxide and extracted with chloroform. Evaporation of the dried extract left *N*-methylpavine as a colourless gum (0·162 g., 100%) which was recovered quantitatively unchanged after being heated with an excess of acetic anhydride for 1·5 hr. When rubbed with anhydrous ether, *N*-methylpavine crystallised as colourless prisms. The m. p. of this base and those of its salts are given in Table 2.

TABLE 2. *Melting points of* N*-methylpavine and its salts.*

	Pyman and Reynolds [a]	Preparation (*a*)	Preparation (*b*)	Mixed m. p. between (*a*) and (*b*)
N-Methylpavine	140—141° (corr.)	135—140°	135—140°	135—140°
Hydrochloride, $8H_2O$ [b]	65—81 (corr.)	72—75	80—82	75—78
Picrate	219 (corr.) [c]	119—121	118—120	118—120
Methiodide, $4H_2O$	118—119 (corr.) sinters 114	118—119 (decomp.) sinters 114	118—120 (decomp.) sinters 114	118—120 (decomp.) sinters 114
Methiodide, $2H_2O$	About 280 (corr.)	—	270—280 (decomp.)	—

[a] *J.*, 1910, **97**, 1320. [b] The m. p. varies with the conditions of drying and with the rate of heating. [c] Probably an error; all our samples melted 100° lower.

(b) *From* 1 : 2-*dihydro*-N-*methylpapaverine.* A solution of this base (0·5 g.), m. p. 129—130° (Schöpf and Thierfelder, *Annalen*, 1932, **497**, 22; Schöpf, *Experientia*, 1949, **5**, 201), in orthophosphoric acid (*d* 1·75; 1 ml.) and 85% formic acid (2·5 ml.) was heated under reflux

at 120° for 25 hr. The cooled mixture was diluted with water (10 ml.) and extracted with ether which removed a trace of non-basic material. After being made strongly alkaline with 2N-sodium hydroxide, the aqueous solution was extracted with chloroform (3 × 25 ml.), and the extracts were washed with water, dried, and distilled to leave a brown gum. This was dissolved in a slight excess of warm 2N-hydrochloric acid, crystallisation of *N*-methylpavine hydrochloride occurring (0·546 g., 72%). The free base, recovered from the hydrochloride by treatment with aqueous ammonia and extraction with chloroform, was crystallised as above. Its m. p. and those of its salts are collected in Table 2.

N-Methylpavine Methosulphate and Methiodide.—1 : 2-Dihydro-*N*-methylpapaverine (15·4 g.) was heated in constant-boiling hydrochloric acid (300 ml.) under nitrogen for 24 hr. The solution was evaporated to dryness under a reduced pressure of nitrogen and after dissolution of the residue in water (10 ml.) the solvent was again evaporated completely. A stirred solution of the residue in the minimum volume of methanol was treated dropwise under nitrogen with aqueous 2N-sodium hydroxide (10 equiv.) and freshly purified dimethyl sulphate (12 equiv.), added simultaneously at such a rate that the pH of the reaction mixture was kept above 10. Crystals started to separate soon after the addition was complete and were collected after 18 hr. (15·0 g.; m. p. 272—276°). The mother-liquor, adjusted to pH 3 by addition of concentrated hydrochloric acid, was concentrated *in vacuo* to one-third volume and a precipitate of inorganic salt was filtered off. A second crop of organic material (3·9 g.), m. p. 265°, slowly separated from the filtrate, and a third crop (3·0 g.), m. p. 265°, was obtained by remethylation of the final mother-liquor with dimethyl sulphate (5 ml.) and aqueous 2N-sodium hydroxide as before. A portion of the first crop, recrystallised twice from aqueous methanol, gave *N-methylpavine methosulphate* as colourless, feathery needles, m. p. 276—278° (Found, in different preparations, all dried at 110°: C, 56·1, 56·2, 56·2; H, 6·4, 6·6, 6·6; N, 2·8. $C_{33}H_{31}O_8NS,\frac{1}{2}H_2O$ requires C, 56·3; H, 6·55; N, 2·8%).

A solution of the combined crops of methosulphate (21·8 g.) in the minimum volume of boiling water was treated with an excess of potassium iodide (8·0 g.). The crystalline precipitate was collected after 15 hr. and dried in air, to afford *N*-methylpavine methiodide tetrahydrate (22 g., 89% overall yield), m. p. 118—120° after sintering at 114° (cf. Table 2).

N-Methylpavinemethine (XI).—Hofmann degradation of *N*-methylpavine methiodide tetrahydrate (5·2 g.) under Pyman's conditions (*J.*, 1915, **107**, 176) afforded *N*-methylpavinemethine, purified as the hydrochloride (3·2 g., 86%), m. p. 204—207°; at 210° decomposition occurred with the evolution of volatile base, presumably dimethylamine. Pyman (*loc. cit.*) records m. p. 205—206° (corr.) for the methine salt. A portion of the methine base, recovered from the hydrochloride, was converted into the picrate. This crystallised from ethanol as yellow needles, m. p. 176—180°, unchanged by repeated recrystallisation. Pyman (*loc. cit.*) reports m. p. 195—196° (corr.).

Dihydro-N-methylpavinemethine (XII).—A solution of *N*-methylpavinemethine hydrochloride (1 g.) and hydrated sodium acetate (1·1 g.; *ca.* 3 equiv.) in ethanol (45 ml.) was shaken with hydrogen and platinic oxide (50 mg.). Uptake of hydrogen (1·0 mol.) was complete in 1·25 hr. After removal of the catalyst, the solution was evaporated to dryness under reduced pressure and the residue was dissolved in water (20 ml.). This solution was acidified to Congo-red, thoroughly extracted with ether, and then made strongly alkaline. The precipitated base was extracted into ether (3 × 50 ml.) and recovered as a colourless glass (0·743 g.) by evaporation of the dried extract. It crystallised from ether to afford *dihydro-N-methylpavinemethine* (XII) as colourless prisms, m. p. 117—119°. A sample was distilled at 130—140°(bath)/0·05 mm., crystallised from ether, and dried at 56° for 2 hr. (Found: C, 71·0; H, 7·6; N, 3·8. $C_{23}H_{29}O_4N$ requires C, 71·1; H, 7·85; N, 3·8%).

Dihydro-N-methylpavinemethine Methiodide (XIII; X = I).—A solution of the foregoing base (3·3 g.) in anhydrous ether (100 ml.) and an excess of methyl iodide (1 ml.) was kept overnight in the dark. The precipitated *methiodide* (XIII; X = I) was collected (4·2 g., 92%) and was recrystallised by dissolving the finely powdered salt in hot methanol then immediately cooling the solution. Pale yellow rods were obtained, having m. p. 188—200° (decomp.), raised by recrystallisation from methanol in the same way to 194—200° (decomp.) (Found, in material dried at 20°: C, 54·1; H, 6·4; I, 24·8. $C_{23}H_{32}O_4NI$ requires C, 53·8; H, 6·3; I, 24·7%).

Dihydropavinebismethine (*2′ : 3′ : 2″ : 3″-Tetramethoxy-1 : 2-5 : 6-dibenzocycloocta-1 : 3 : 5-triene*) (XIV).—A solution of the foregoing methiodide (4·2 g.) in 50% aqueous methanol (200 ml.) was shaken with moist silver oxide (from 10 g. silver nitrate) for 45 min. and then filtered. The clear filtrate and washings, now free from iodide ion, were concentrated below

40° under reduced pressure to *ca.* 80 ml. Potassium hydroxide (80 g.) was added; a colourless oil separated which increased in amount as the solution was heated under reflux for 5 hr. The volatile base evolved during this period was collected in dilute hydrochloric acid and identified as trimethylamine by conversion into the picrate, m. p. and mixed m. p. 217°.

The oil present in the main reaction mixture was extracted with ether (3 × 150 ml.), and the extract was washed with water, twice with dilute hydrochloric acid, and finally with water. Evaporation of the dried ethereal solution left a crystalline residue of *dihydropavinebismethine* (XIV) (2·26 g., 86%), m. p. 152—154°. It formed glistening plates, m. p. 154—156°, from ethanol (Found, in material dried at 110° : C, 73·5; H, 7·0. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

The basic fraction (0·15 g.) separated when the acidic extracts above were made alkaline, and was isolated by ether extraction as usual. Recrystallised from ether, it had m. p. 113—119° raised to 114—120° in admixture with an authentic sample of dihydro-*N*-methylpavinemethine (XII).

2′ : 3′ : 2″ : 3″-Tetramethoxy-1 : 2-5 : 6-dibenzocycloocta-1 : 5-diene (XIX).—The foregoing product, previously dried at 110° *in vacuo*, was shaken in ethanol (10 ml.) with platinic oxide (10 mg.) and hydrogen at room temperature and atmospheric pressure. The uptake of hydrogen (0·97 mol.) was complete in 3 hr. After removal of the catalyst, the solution was concentrated. The *dibenzocyclooctadiene* separated as colourless plates, m. p. 198—200° raised by recrystallisation from ethanol and sublimation at 145—160° (bath)/0·01 mm. to 201—203° (Found : C, 73·1; H, 7·3. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%).

2 : 2′-Dicarboxy-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (XV).—A solution of 2 : 2′-diacetyl-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (0·266 g.) (Battersby and Binks, following paper) in dioxan (20 ml.) was oxidised with alkaline sodium hypochlorite (6 ml.) as described for the preparation of 2-carboxy-4 : 5 : 3′ : 4′-tetramethoxydibenzyl (Battersby and Binks, *loc. cit.*). The acidic fraction crystallised from glacial acetic acid, to afford the *dicarboxylic acid* (XV) as colourless needles (0·231 g., 93%), m. p. 310—312° (decomp.) unchanged by further recrystallisation (Found : C, 61·3; H, 5·6%; equiv. 185. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·7%; equiv. 195).

Heating the acid (0·1 g.) in methanol (60 ml.) and concentrated sulphuric acid (1 ml.) for 24 hr., concentration to one-third volume under reduced pressure, filtration whilst hot, and cooling gave the *dimethyl ester* (XVII) as long, colourless needles (40 mg.), m. p. 176—178°, raised to 182—185° by recrystallisation from methanol (Found : C, 63·4; H, 6·3. $C_{22}H_{26}O_8$ requires C, 63·1; H, 6·3%).

Oxidation of Dihydropavinebismethine (XIV).—Potassium permanganate (1·174 g.; equiv. to 6 O) in acetone (160 ml.) and water (80 ml.) was added during 2 hr. to a stirred solution of dihydropavinebismethine (0·599 g.) in acetone (100 ml.) at 50°. The oxidising agent had been largely consumed by the end of the addition. Next morning the slight excess of permanganate was destroyed with aqueous hydrogen peroxide and the manganese dioxide removed. The filter pad was extracted with boiling acetone (2 × 50 ml.) and boiling 0·01N-sodium hydroxide (2 × 50 ml.), and the washings were combined with the main aqueous solution. This was concentrated under reduced pressure until free from acetone and then extracted with ether (3 × 100 ml.) to afford the neutral fraction (*A*) (0·15 g.) which was recovered from the dried ethereal solution by evaporation. The aqueous layer was acidified to Congo-red, a gel forming which was coagulated by heat. The solid was collected, dried *in vacuo*, and recrystallised twice from glacial acetic acid. 2 : 2′-Dicarboxy-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (XV) separated as colourless needles (0·43 g., 60%), m. p. 310—312° (decomp.) unchanged in admixture with the sample prepared as above. A portion was converted into the dimethyl ester, identical with authentic (XVII) in crystal form, m. p., and mixed m. p.

The neutral fraction *A* crystallised from a large volume of ethanol to give colourless needles (85 mg.), m. p. 242—244° raised to 252—254° by repeated recrystallisation from the same solvent (Found, in material dried at 110° : C, 66·9, 67·1; H, 5·3, 5·8. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·7%). This *substance* gave (*a*) a deep red 2 : 4-dinitrophenylhydrazone, (*b*) no colour reaction with *o*-dianisidine under conditions which gave a strong yellow colour with veratraldehyde, and (*c*) a brownish-yellow colour when a portion (9·7 mg.) was heated under reflux with *o*-phenylenediamine (6 mg.) in ethanol (6 ml.), and glacial acetic acid (1 drop) for 4 hr. (no phenazine derivative could be isolated).

Hydrogenolysis of Dihydro-N-methylpavinemethine Methochloride (XIII; X = Cl).—A solution of the methiodide (XIII; X = I) (0·406 g.) in 50% aqueous ethanol (140 ml.) was shaken for 2 hr. with freshly prepared silver chloride (from 0·41 g. of silver nitrate). The silver salts were then filtered off and washed with ethanol. The filtrate and washings, now free from iodide ion, were shaken with 10% palladium–charcoal (0·5 g.) and hydrogen for 1·5 hr. After

removal of the catalyst, the solution was concentrated under reduced pressure, the dibenzo*cyclo*octadiene (XIX) separating (40 mg.; m. p. 200—203°, raised to 202—203° in admixture with the earlier preparation).

Reductive Fission of N-*Methylpavine Methochloride*.—The methochloride of *N*-methylpavine (X), prepared from the related methiodide by Pyman's method (*J.*, 1910, **97**, 1320), was dried at 100°/0·05 mm. for 1·5 hr. and a portion (0·130 g.) was suspended in anhydrous liquid ammonia (15 ml.). Sodium was added until a blue colour was obtained which faded only slowly. After cautious addition of water (20 ml.), the mixture was poured into water (100 ml.) and extracted with ether (3 × 50 ml.). Evaporation of the dried extract left a colourless gum (0·109 g.) which crystallised completely on being seeded with dihydro-*N*-methylpavinemethine (XII). The m. p. of the product, 117—119°, was unchanged by further recrystallisation or by admixture with the earlier preparation of (XII).

Hofmann Degradation of N-*Methylpavinemethine Methiodide* (XX; X = I).—A suspension of the methiodide (2·58 g.), prepared from *N*-methylpavinemethine as described by Pyman (*J.*, 1915, **107**, 176), in water (180 ml.) was shaken with moist silver oxide from 4 g. of silver nitrate until the solution was free from iodide ion. Potassium hydroxide (200 g.) was added to the filtered solution (200 ml.), which was then heated under reflux for 5 hr. The volatile base evolved was collected in dilute hydrochloric acid and identified as trimethylamine by conversion into the picrate, m. p. and mixed m. p. 217°. The neutral fraction (1·49 g.) from the main aqueous solution was isolated as in the preparation of dihydropavinebismethine. A portion of it, recrystallised twice from benzene, afforded the alcohol (XXI; R = OH) as nodules, m. p. 145—146°. The analytical sample was sublimed at 180°(bath)/5 × 10^{-4} mm. (Found: C, 70·3; H, 6·4; active H, 0·37. Calc. for $C_{20}H_{23}O_5$: C, 70·2; H, 6·5; active H, 0·29%). Pyman (*loc. cit.*) records m. p. 147—148° (corr.).

Decomposition of N-*Methylpavinemethine Methohydroxide* (XX; X = OH).—The corresponding methiodide (0·25 g.) was converted into the methohydroxide as in the preceding experiment, and the solution (15 ml.) was heated under reflux. A gum separated rapidly on the sides of the flask and after 15 min. the cooled solution was decanted from the gum which was washed with water and dried *in vacuo* (138 mg., 83%). The decanted solution was heated under reflux for a further 1 hr., cooled, and extracted with ether. Evaporation of the dried ethereal solution left a gum (19 mg., 11%). When the final aqueous solution was evaporated to dryness, only 4 mg. of residue remained. Crystallisation of the combined gummy fractions from benzene afforded the alcohol (XXI; R = OH) (128 mg.), m. p. 145—146° alone or in admixture with the foregoing product.

2′ : 3′ : 2″ : 3″-*Tetramethoxy*-1 : 2-5 : 6-*dibenzo*cyclo*octatetraene* (XXII).—A solution of the alcohol (0·34 g.) obtained in the foregoing experiment, in rigorously purified dioxan (10 ml.) and aqueous 4N-sulphuric acid (10 ml.), was heated under reflux for 6 hr. After removal of the dioxan under reduced pressure, the solution was extracted with ether (3 × 50 ml.), and the combined extracts were washed with aqueous sodium hydroxide and water. Evaporation of the ether left a gum (0·235 g.) which was dissolved in benzene and run on to a column of alumina. Elution with benzene (80 ml.) followed by ether–benzene (1 : 9; 60 ml.) gave the *dibenzo*cyclo*octatetraene* (XXII) as colourless needles (37 mg., 11%), m. p. 159—164°, as the first fraction; later fractions were only semi-crystalline. The crystalline material was recrystallised from benzene for analysis (Found: C, 73·7; H, 6·5. $C_{20}H_{20}O_4$ requires C, 74·0; H, 6·2%). A solution of the dibenzo*cyclo*octatetraene (14·05 mg.) in ethanol (12·5 ml.) was shaken with hydrogen and platinum. Uptake of hydrogen proceeded smoothly, but ceased abruptly when crystallisation of the reduction product occurred on the catalyst. At this point, 1·54 ml. had been absorbed (theory for 2 mols., 2·08 ml.). The catalyst was filtered off from the hot solution and, on cooling, crystallisation again occurred to afford the dibenzo*cyclo*octadiene (XIX), m. p. and mixed m. p. 197—201°.

Decomposition of Dihydro-N-*methylpavinemethine Methiodide* (XIII; X = I).—A solution of the methiodide (207 mg.) in water (9 ml.) was heated under reflux for 4 hr., diluted with water (15 ml.), cooled, and extracted several times with ether, each extract being washed once with water. The combined aqueous solutions were concentrated under reduced pressure to 8 ml. and the crystals which separated were collected (132 mg., 64%). This material contained ionic iodine and had m. p. 190° alone or in admixture with the starting material. The ethereal extracts, after being dried and evaporated, afforded a gum (44 mg., 32%) which crystallised from ethanol to give the *alcohol* (XXIII) as colourless compact prisms, m. p. 177—179° (Found: C, 69·3; H, 6·8; I, 0. $C_{20}H_{24}O_5$ requires C, 69·7; H, 7·0%).

Hydrogenation of the Alcohol (XXI; R = OH).—This alcohol (118 mg.) was shaken in ethanol

(30 ml.) with hydrogen and platinic oxide until the uptake was complete. After removal of the catalyst, the solution was concentrated to low volume. The dihydro-alcohol (XXIII) crystallised, m. p. 172—176° raised to 174—177° in admixture with the foregoing product.

Dehydration of the Dihydro-alcohol (XXIII).—A solution of the dihydro-alcohol (0·25 g.) in purified dioxan (10 ml.) and aqueous 4N-sulphuric acid (10 ml.) was heated under reflux for 3 hr. Crystals of dihydropavinebismethine (XIV) (96 mg., 40%) separated from the cooled solution. These recrystallised from ethanol as colourless plates, m. p. 152—154° alone or in admixture with the sample of (XIV) prepared earlier (m. p. 152—154° in the same bath). A portion (52·6 mg.) of this product was reduced in alcohol with hydrogen and platinum, and the product, isolated in the usual way, was the dibenzo*cyclo*octadiene (XIX), m. p. and mixed m. p. 196—200°.

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*The Synthesis of 2′ : 3′ : 2″ : 3″-Tetramethoxy-*1 : 2-4 : 5-*dibenzocyclohepta-*1 : 4-*dienes and Related Compounds.*

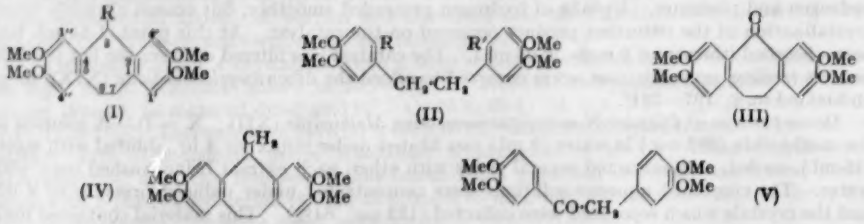
By ALAN R. BATTERSBY and R. BINKS.

[Reprint Order No. 6377.]

3 : 4 : 3′ : 4′-Tetramethoxydibenzyl reacts with aldehydes under strongly acidic conditions to give derivatives of 2′ : 3′ : 2″ : 3″-tetramethoxy-1 : 2-4 : 5-dibenzo*cyclo*hepta-1 : 4-diene (I; R = H) in good yield. An alternative route to these compounds involves the preparation and cyclisation of 2-carboxy-4 : 5 : 3′ : 4′-tetramethoxydibenzyl. The products from the two routes have been correlated. A new reaction of sodium bismuthate is recorded briefly.

OUR interest in the degradation products from pavine (Battersby and Binks, preceding paper) led us to prepare certain derivatives of the tetramethoxydibenzo*cyclo*heptadiene (I; R = H). The analogous compound lacking the methoxyl groups and some derivatives of it have been prepared from 1 : 2-4 : 5-dibenzo*cyclo*hepta-1 : 4-dien-3-one, which is available by cyclisation of 2-carboxydibenzyl (Cope and Fenton, *J. Amer. Chem. Soc.*, 1951, **73**, 1673; Treibs and Klinkhammer, *Ber.*, 1951, **84**, 671).

In the methoxylated series, one synthesis of compounds of type (I) takes advantage of the activated state of the aromatic nuclei in 3 : 4 : 3′ : 4′-tetramethoxydibenzyl (II; R = R′ = H) towards electrophilic reagents. Thus, acetaldehyde and the ether (II; R = R′ = H) condensed at room temperature in the presence of concentrated sulphuric acid, giving the methyldibenzo*cyclo*heptadiene (I; R = Me) in 60% yield. The molecular



weight of this material eliminated possible structures for it which involve macrocyclic rings (cf. Bergmann and Pelchowicz, *J. Amer. Chem. Soc.*, 1953, **75**, 4281). 2 : 2-Dimethoxyethylamine and 2 : 2-dimethoxyethyl-*NN*-dimethylamine with the tetramethoxydibenzyl (II; R = R′ = H) similarly gave good yields of basic products which were

assigned the structures (I; R = CH_2·NH_2 and CH_2·NMe_2 respectively). This method can clearly be extended to afford 1 : 2-4 : 5-dibenz*ocyclo*hepta-1 : 4-dienes from those derivatives of dibenzyl which carry 3- and 3′-alkoxyl groups and have the 6- and the 6′-position available.

In a second route to the tricyclic series the last step follows the work of Cope and Fenton and of Treibs and Klinkhammer (*locc. cit.*). 3 : 4 : 3′ : 4′-Tetramethoxydibenzyl and acetyl chloride in the presence of aluminium chloride gave smoothly a mixture of 2-acetyl-4 : 5 : 3′ : 4′-tetramethoxydibenzyl (II; R = Ac, R′ = H) and 2 : 2′-diacetyl-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (II; R = R′ = Ac) which were separated by virtue of their different solubilities in ethanol. These structures can be assigned with confidence, since the 3 : 4-dimethoxy-derivatives of toluene and ethylbenzene are acylated at the 6-position under the conditions of the Friedel–Crafts reaction (Fargher and Perkin, *J.*, 1921, **119**, 1724; Shinoda and Sato, *J. Pharm. Soc. Japan*, 1927, **548**, 860). Oxidation of the monoketone with alkaline sodium hypochlorite yielded 2-carboxy-4 : 5 : 3′ : 4′-tetramethoxydibenzyl (II; R = CO_2H, R′ = H) which with phosphorus pentachloride gave the corresponding acid chloride. This was cyclised at room temperature with aluminium chloride in nitrobenzene to give the *cyclo*heptadienone (III); two crystalline forms of this ketone were isolated and found to be readily interconvertible. An attempt to prepare it from 3 : 4 : 3′ : 4′-tetramethoxydibenzyl and carbon tetrachloride by the procedure used for benzophenone (*Org. Synth.*, **8**, 26) gave a high recovery of starting material.

The overall yield of the ketone (III) from the second series of reactions was low and in order to relate the products from the two routes, it was decided to degrade the materials from the aldehyde condensation to the ketone (III) rather than attempt the synthesis of the former from the latter.

The methiodide derived from the tertiary base (I; R = CH_2·NMe_2) was degraded by Hofmann's method to give a homogeneous nitrogen-free product (IV). This was readily hydrogenated to a crystalline dihydro-derivative, identical with the product (I; R = Me) obtained from acetaldehyde with 3 : 4 : 3′ : 4′-tetramethoxydibenzyl. Warm potassium permanganate in acetone slowly oxidised the Hofmann product (IV), and the neutral fraction afforded the same dibenz*ocyclo*heptadienone (III) which had been obtained as above. This ketone did not react with 2 : 4-dinitrophenylhydrazine, in agreement with Buchanan's finding on the related dibenz*ocyclo*heptadienone lacking the methoxyl groups (*Chem. and Ind.*, 1952, 855).

Before the nature of the oxidation product from the ether (IV) was known, it was treated with sodium bismuthate in glacial acetic acid as a test for a glycol residue (Rigby, *J.*, 1950, 1907). One mol. of the reagent was consumed at room temperature in 2 hr., a result of some interest now that the structure of the starting material is known. Sodium bismuthate also attacked 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (V) and *o*-dimethoxybenzene at room temperature, and the neutral products from the latter, after hydrogenation and alkaline hydrolysis, gave a very small yield of adipic acid. Anisole was attacked slowly under the conditions used above. A careful study of this reaction is desirable,

Ultraviolet absorption maxima (mμ) *in ethanol* (ε *in parentheses*).

3 : 4 : 3′ : 4′-Tetramethoxydibenzyl (II; R = R′ = H)	230 (17,620)	280 (6470)	
2-Acetyl-4 : 5 : 3′ : 4′-Tetramethoxydibenzyl (II; R = Ac, R′ = H)	231 (30,690)	276 (11,220)	304 (5120)
2 : 2′-Diacetyl-4 : 5 : 4′ : 5′-Tetramethoxydibenzyl (II; R = R′ = Ac)	234 (43,700)	273 (17,060)	306 (10,100)
3 : 4 : 3′ : 4′-Tetramethoxydeoxybenzoin (V)	230 (24,150)	276 (14,000)	305 (9620)
The dibenz*ocyclo*heptadiene (II; R = CH_2·NMe_2)	285 (7870)		
The dibenz*ocyclo*heptadienone (III)	245 (13,500)	292 (11,500)	346 (11,800)
The methylenedibenz*ocyclo*heptadiene (IV)	261 (11,780)	291 (8630)	

but these preliminary results are presented in view of the use of sodium bismuthate as a diagnostic test for glycol and related groupings.

The ultraviolet absorption spectra of our materials (see Table) are in agreement with the structures presented above.

Experimental

Analyses are by Mr. B. S. Noyes of Bristol.

3 : 4 : 3′ : 4′-*Tetramethoxydibenzyl* (II; R = R′ = H).—3 : 4 : 3′ : 4′-Tetramethoxydeoxybenzoin (V) (Kubiczek, *Monatsh.*, **1946**, **76**, 55) was reduced by the method Erdtman employed with 3 : 4 : 3′ : 4′-tetramethoxybenzil (*Annalen*, **1933**, **505**, 198), save that the reduction period was increased to 1·5 hr. The product (62%) had m. p. 108—110°; Erdtman (*loc. cit.*) records 109—110°.

2-*Acetyl*-4 : 5 : 3′ : 4′-*tetramethoxydibenzyl* (II; R = Ac, R′ = H) ***and*** **2 : 2′-*Diacetyl*-4 : 5 : 4′ : 5′-*tetramethoxydibenzyl*** (II; R = R′ = Ac).—The foregoing product (5 g.) in anhydrous benzene (150 ml.) was stirred at room temperature with powdered anhydrous aluminium chloride (4·4 g.) whilst acetyl chloride (2·6 ml., 2 equiv.) in benzene (70 ml.) was added during 1 hr. After being stirred for a further 1 hr., the mixture was heated to the b. p. during 0·5 hr. and then for 2 hr. under reflux. The cooled suspension was poured on ice, and the complex was decomposed as usual with hydrochloric acid. The insoluble matter (*A*) (0·835 g.), m. p. 171—175°, was collected and the clear filtrate was extracted thrice with benzene. The combined extracts were washed with water, dilute sodium hydroxide, and water, then dried (Na_2SO_4) and evaporated to a semi-crystalline gum (6·25 g.). When the alkaline extract was acidified, only a trace of phenolic material (*ca.* 0·2 g.) separated. The main gummy fraction partly crystallised from ethanol to yield a mother-liquor (*B*) and a crop of crystals (1·25 g.), m. p. 169—170°. The latter was combined with the insoluble matter *A* and recrystallised from ethanol; **2 : 2′-*diacetyl*-4 : 5 : 4′ : 5′-*tetramethoxydibenzyl*** (II; R = R′ = Ac) was obtained as colourless rods (1·83 g., 28%), m. p. 173—175°, after slight sintering at 166° (Found, in material dried at 100°: C, 68·7; H, 6·9. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·8%). It afforded a dark red 2 : 4-dinitrophenylhydrazone. A sample (3·2 mg.) in ethanol (12·5 ml.) was shaken with 10% palladium–charcoal (50 mg.) and hydrogen at room temperature and pressure; the uptake (0·86 ml.; 4 mol. = 0·79 ml.) was complete in 1 hr.

When the alcoholic mother-liquor *B* was concentrated, impure starting material separated (1·02 g.; m. p. 90—103°, raised to 105—109° on admixture with an authentic sample). Evaporation of the final mother-liquor left a gum which was fractionated in a short-path still. A colourless oil distilled at 120—130° (bath)/20 mm. and was identified as acetophenone by its 2 : 4-dinitrophenylhydrazone. The second fraction distilled at 160—180° (bath)/0·01 mm. as a yellow oil which crystallised on addition of ether. This solid was adsorbed from benzene–light petroleum on to a column of alumina and then was eluted with ether–benzene (1 : 1). After a first fraction consisting of 3 : 4 : 3′ : 4′-tetramethoxydibenzyl, **2-*acetyl*-4 : 5 : 3′ : 4′-*amethoxydibenzyl*** (II; R = Ac, R′ = H) was obtained (0·76 g., 13%). It crystallised from aqueous ethanol as colourless needles, m. p. 96—98° (Found, in material dried at 65°: C, 69·7; H, 6·8. $C_{20}H_{24}O_5$ requires C, 69·8; H, 7·0%). This product gave a dark red 2 : 4-dinitrophenylhydrazone.

2-*Carboxy*-4 : 5 : 3′ : 4′-*tetramethoxydibenzyl* (II; R = CO_2H, R′ = H).—A solution of sodium hypochlorite was prepared by passing chlorine (3·2 g.) into a solution of sodium hydroxide (4·4 g.) in water (30 ml.) at 0°. A portion (3·5 ml.) was warmed to 55° and added to a solution of the monoketone (0·157 g.) in rigorously purified dioxan (10 ml.). Addition of water (10 ml.) gave a clear solution which was warmed at 60—70° for 1·5 hr. After the dioxan had been evaporated under reduced pressure, the mixture was freed from hypochlorite ion by the addition of aqueous sodium metabisulphite and was then acidified to Congo-red with concentrated hydrochloric acid. The crystalline precipitate was collected and redissolved in dilute aqueous sodium hydroxide, and the filtered solution was acidified once more to afford the ***carboxylic acid*** as colourless compact prisms (0·12 g., 76%), m. p. 159—160°, raised to 161—164° by recrystallisation from ethanol (Found, in material dried at 100°: C, 65·4; H, 6·2%; equiv., 350. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%; equiv., 346).

2′ : 3′ : 2″ : 3″-*Tetramethoxy*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*dien*-3-*one* (III).—(a) ***By cyclisation of the acid*** (II; R = CO_2H, R′ = H). A suspension of the foregoing acid (0·108 g.) and phosphorus pentachloride (78 mg., 1·2 equiv.) in dry nitrobenzene (12 ml.) was stirred at room temperature for 1 hr. Powdered anhydrous aluminium chloride (85 mg., 2 equiv.) was then added and the deep red solution was kept for 2 days. After addition of 2N-hydrochloric acid (5 ml.), the solvent was distilled in steam, to leave a suspension of gum in water. This was made alkaline with 2N-sodium hydroxide (10 ml.), and the gum was dissolved by addition of acetone. When the acetone was removed under reduced pressure, the neutral fraction separated

as pale yellow needles which were recrystallised twice from ethanol, to give the *dibenzo*cyclo*heptadienone* (III) (48 g., 47%) (Found, in material dried at 100° : C, 69·5; H, 6·2. $C_{18}H_{20}O_5$ requires C, 69·5; H, 6·15%). The first preparation of this ketone had m. p. 128·5—129°, but later samples melted consistently at 142—143° with a transition at 128—129°. When the needles were kept in contact with ethanol for several days, they changed to compact prisms, m. p. 141—143°. Recrystallisation of the latter from ethanol afforded needles with m. p. behaviour as above.

Slightly impure starting material (55 mg.), m. p. 154—156°, raised to 158—160° on admixture with an authentic sample, was recovered by acidification of the aqueous alkaline filtrate.

Attempted preparations of the ketone (III) in which thionyl chloride was used under a variety of conditions to convert the acid into its chloride were unsuccessful, as was direct cyclisation of the acid with concentrated sulphuric acid (cf. Haworth and Mavin, *J.*, 1931, 1363).

(b) *By oxidation of the methylene derivative* (IV). A stirred solution of this derivative (0·178 g.) in acetone (100 ml.) was unaffected at room temperature by part of a solution of potassium permanganate (0·35 g.; equiv. to 6 O) in acetone (52 ml.) and water (26 ml.). Oxidation occurred under reflux and all the remaining oxidising agent was added dropwise during 1·5 hr. After being heated and stirred for a further 1·5 hr., the solution, now colourless, was filtered and the filter pad was washed with hot water and boiling acetone. The clear filtrate was freed from acetone under reduced pressure and the precipitated solid was collected (0·134 g.). This crystallised from ethanol to give the ketone (III) as pale yellow needles (77 mg.), m. p. 142—143° with a transition at 126°, unchanged on admixture with the foregoing product. The prismatic modification was obtained as before and was identical with that prepared as above.

Ozonolysis of a solution of the derivative (IV) in ethyl chloide at −78° gave a brown neutral fraction from which the ketone (III) could not be isolated.

2 : 2-*Dimethoxyethyl*-NN-*dimethylamine*.—Dimethylamine, prepared from the hydrochloride (300 g.), was carried in nitrogen through a column of barium oxide and into a solution of 2 : 2-dimethoxyethyl chloride (31 g.) in absolute methanol (400 ml.). The mixture was heated at 140° for 12 hr. in an autoclave and was worked up as described by Woodward and Doering (*J. Amer. Chem. Soc.*, 1945, **67**, 860). The acetal (5·5 g., 17%) had b. p. 80—81°/112 mm. With methyl iodide in ether it gave the methiodide as rods (from acetone), m. p. 126—127° to a resin which flowed at 133—134°. Fourneau and Chantalou (*Bull. Soc. chim. France*, 1945, **12**, 845) record m. p. 126°.

2′ : 3′ : 2″ : 3″-*Tetramethoxy*-3-*methyl*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*diene* (I; R = Me). —(*a*) Paraldehyde (0·192 g.) in glacial acetic acid (3 ml.) was added during 0·5 hr. to a stirred solution of 3 : 4 : 3′ : 4′-tetramethoxydibenzyl (1·3 g.) in glacial acetic acid (25 ml.) and concentrated sulphuric acid (15 ml.) at room temperature. After being stirred for a further 2 hr., the solution was poured on ice, and the insoluble matter was crystallised from ethanol. The *dibenzo*cyclo*heptadiene* (I; R = Me) separated as colourless blades (0·845 g., 60%), m. p. 126—128° unchanged by further recrystallisation or by sublimation at 100—135° (bath)/0·05 mm. [Found, for sublimed material: C, 73·0; H, 7·3%; *M* (in camphor), 281. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%; *M*, 328].

(*b*) A solution of the Hofmann degradation product (IV) (38·8 mg.) in ethanol (10 ml.) was shaken with hydrogen and platinic oxide (10 mg.). Hydrogen (1 mol.) was absorbed during 9 hr. After removal of the catalyst, the solution was concentrated. The diene (I; R = Me) crystallised and had m. p. 127—129° unchanged on admixture with the foregoing product.

3-*Dimethylaminomethyl*- *and* 3-*Aminomethyl*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*diene* (I; R = CH_2·NMe_2) *and* (I; R = CH_2·NH_2).—A solution of 3 : 4 : 3′ : 4′-tetramethoxydibenzyl (0·5 g.) and 2 : 2-dimethoxyethyl-*NN*-dimethylamine (0·25 g.) in glacial acetic acid (10 ml.) was treated with concentrated sulphuric acid (3 ml.), kept for 15 hr., and then poured on ice. Extraction of the aqueous solution with benzene removed only a trace of neutral matter. The aqueous layer was made strongly alkaline with sodium hydroxide, and the precipitated crystalline base (0·506 g.) was collected and washed with water. It recrystallised from aqueous methanol, to afford the 3-*dimethylaminomethyl compound* (I; R = CH_2·NMe_2) as colourless plates (0·385 g., 62%), m. p. 136—138° [Found, in material dried at 100°: C, 71·5; H, 7·7; N, 4·0%; *M* (in benzene), 368. $C_{22}H_{29}O_4N$ requires C, 71·1; H, 7·9; N, 3·8%; *M*, 371].

(With P. S. Uzzell.) By replacing the *NN*-dimethyl-acetal above with 2 : 2-dimethoxyethylamine (Woodward and Doering, *loc. cit.*), the 3-*aminomethyl analogue* (I; R = CH_2·NH_2) was prepared. It crystallised from aqueous ethanol as colourless plates, m. p. 129—130°

(Found, in material dried at 78° : C, 66·6; H, 7·5; N, 3·9; H_2O, 4·8. $C_{20}H_{25}O_4N,H_2O$ requires C, 66·5; H, 7·5; N, 3·9; H_2O, 5·0%).

Hofmann Degradation of the Base (I; R = CH_2·NMe_2).—A suspension of this base (0·38 g.) in anhydrous ether (20 ml.) was treated with sufficient methanol to give a clear solution and then with methyl iodide (1 ml.). After 2 days, the precipitated *methiodide* (0·503 g., 95%), m. p. 280—282° (decomp.), was collected. It crystallised from methanol as feathery needles of the same m. p. (Found, in material dried at 100° : C, 53·5; H, 6·2. $C_{23}H_{32}O_4NI$ requires C, 53·8; H, 6·3%).

Moist silver oxide (from 2 g. of silver nitrate) was shaken with a solution of the methiodide (0·46 g.) in 50% aqueous methanol (170 ml.) until the precipitation of iodide was complete (45 min.). The filtered solution and washings were concentrated at room temperature under reduced pressure to remove the methanol. Potassium hydroxide (90 g.) was added to the aqueous solution which was then heated under reflux for 2·5 hr. Trimethylamine was rapidly evolved and an oil separated. The latter was extracted into ether, and the extract washed with water, dilute hydrochloric acid, and water. Evaporation of the dried ether solution left a crystalline residue (0·271 g., 91%), m. p. 182—187°, which, recrystallised thrice from ethanol, gave the 2′ : 3′ : 2″ : 3″-*tetramethoxy*-3-*methylene*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*diene* (IV) as plates, m. p. 184—187° (Found, in material dried at 100° : C, 73·3; H, 6·5. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

Action of Sodium Bismuthate on o-*Dimethoxybenzene.*—A solution of *o*-dimethoxybenzene (5 g.) in glacial acetic acid (50 ml.) was shaken at room temperature with sodium bismuthate (15 g.) until the latter had been reduced (10 hr.). A second portion of sodium bismuthate (total 26 g., 2 mol. based on 80% purity) was consumed in the same way during a further 24 hr. The dark mixture was treated with phosphoric acid (*d* 1·75; 5·2 ml.), and the products were extracted into ether. After being shaken with an excess of aqueous potassium carbonate, the extract was dried and evaporated, to leave a brown oil (2·5 g.). This was hydrogenated at room temperature and pressure in ethanol, in the presence of platinum; uptake of hydrogen (220 ml.) ceased after 2 hr. The recovered reduced material was heated under reflux for 3 hr. with methanolic N-potassium hydroxide (100 ml.), and the methanol was removed under reduced pressure. A solution of the residue in water was acidified, made alkaline with potassium carbonate, extracted with ether, and finally acidified to Congo-red. Continuous extraction of this solution with ether afforded adipic acid (*ca.* 100 mg.) which was purified by sublimation at 110°/0·05 mm. and had m. p. and mixed m. p. 149—153°.

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Perfluoroalkyl Derivatives of Sulphur. Part II. Trifluoromethanesulphonic, -sulphinic, and -sulphenic Acid and the Infrared Spectra of Compounds Containing* $-SO_2-$ *and* $>S{:}O$ *Groups.*

By R. N. Haszeldine and J. M. Kidd.

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Trifluoromethanesulphonyl chloride is prepared by oxidation of the sulphenyl chloride with chlorine and water, or from trifluoromethanesulphonic acid and phosphorus pentachloride. The sulphonic acid is obtained from carbon disulphide in 80% yield. Reduction of trifluoromethanesulphonyl chloride with zinc gives trifluoromethanesulphinic acid, isolated as its sodium and zinc salts. Hydrolysis of trifluoromethanesulphenyl chloride gives trifluoromethanesulphenic acid only as unstable intermediate, and bistrifluoromethyl disulphide and trifluoromethanesulphinic acid are the main products; control of the reaction conditions enables trifluoromethyl trifluoromethanethiolsulphonate to be obtained instead of the sulphinic acid. The mechanism of the hydrolyses of trifluoromethanesulphenyl chloride, trifluoromethyl trifluoromethanethiolsulphonate, and bistrifluoromethyl disulphide are discussed.

Infrared spectra of sulphonyl and sulphuryl halides, sulphones, thiolsulphonates, metal sulphonates, thionyl halides, sulphoxides, sulphites, and metal sulphinates are correlated and discussed.

Trifluoromethane-thiol, -sulphenyl chloride, and -sulphonic acid were described earlier; * studies on the preparation of the related trifluoromethane-sulphinic and -sulphenic acid are now described.

Aliphatic sulphinic acids are unstable compounds usually prepared by reaction of sulphur dioxide with a Grignard reagent or by reduction of a sulphonyl chloride; they decompose in air, particularly when heated, to give the corresponding sulphonic acid and thiolsulphonate (von Braun and Weissback, *Ber.*, 1930, **63**, 2836), $3R{\cdot}SO_2H \longrightarrow R{\cdot}SO_3H + R{\cdot}SO_2{\cdot}SR + H_2O$, and are usually isolated as sodium, barium, magnesium, or zinc salts. Salts of trichloromethanesulphinic acid have been prepared by reaction of the sulphonyl chloride with potassium cyanide, sulphur dioxide, or potassium sulphite; they are all water-soluble, but decompose when heated. In view of the experimental difficulties associated with perfluoroalkyl Grignard reagents (*J.*, 1952, 3423; 1953, 1748; 1954, 1273) the route to trifluoromethanesulphinic acid from trifluoromethanesulphonyl chloride was chosen.

Trifluoromethanesulphonyl chloride was synthesised by two methods: from trifluoromethanesulphonic acid by reaction with phosphorus pentachloride, and by oxidation of trifluoromethanesulphenyl chloride. Reaction of the sulphenyl chloride with hydrogen peroxide gives a mixture of bistrifluoromethyl disulphide and trifluoromethanesulphonyl chloride which is difficult to separate. The sulphenyl chloride is readily oxidised by a mixture of chlorine and water at room temperature, however, and this provides an excellent method of synthesis:

$$CF_3{\cdot}SCl + 2Cl_2 + 2H_2O \longrightarrow CF_3{\cdot}SO_2Cl + 4HCl$$

Trifluoromethanesulphonyl chloride is formed quantitatively provided that the chlorine present is in excess of that required by the above equation. This reaction is analogous to the preparation of trichloromethanesulphonyl chloride from carbon disulphide; chlorine yields trichloromethanesulphenyl chloride which in presence of water is oxidised to the sulphonyl chloride (Kolbe, *Annalen*, 1845, **54**, 155). Trifluoromethanesulphonyl chloride is a colourless liquid, b. p. 31·6°, which is almost insoluble in water and only very slowly hydrolysed by it at room temperature. At higher temperatures it is converted into the

* Part I, *J.*, 1954, 4228, where references to related work are given.

sulphonic acid within a few hours; hydrolysis by aqueous sodium hydroxide is very rapid, even at room temperature. In this way trifluoromethanesulphonic acid can be synthesised from carbon disulphide by way of bistrifluoromethyl disulphide without the preparation of the bistrifluoromethylthiomercury used in the original synthesis of the acid (Part I, *loc. cit.*):

$$CS_2 \xrightarrow{IF_5} CF_3{\cdot}S_2{\cdot}CF_3 \xrightarrow{Cl_2} CF_3{\cdot}SCl \xrightarrow{Cl_2\text{–}H_2O} CF_3{\cdot}SO_2Cl \longrightarrow CF_3{\cdot}SO_3H$$

The overall yield from carbon disulphide is >80%, since the last three steps are quantitative.

When trifluoromethanesulphenyl chloride is treated with water and less chlorine than that required by the penultimate stage, bistrifluoromethyl disulphide is also formed, and as the amount of chlorine is progressively decreased so is the yield of trifluoromethanesulphonyl chloride until finally, when no chlorine is present, no sulphonyl chloride is produced; the products formed under such conditions are discussed below.

Reaction of trifluoromethanesulphonyl chloride with zinc dust and water in absence of air, followed by treatment of the resulting aqueous solution with sodium carbonate, gives sodium trifluoromethanesulphinate as a monohydrate. Monohydrate formation is in accord with sodium salts of other sulphinic acids which have general formula $R{\cdot}SO_2Na,H_2O$. The salt is deliquescent and readily soluble in acetone or alcohol. Attempts to isolate a zinc salt of the sulphinic acid less hydrated than $(CF_3{\cdot}SO_2)_2Zn,3H_2O$ have so far been unsuccessful. The infrared spectrum of sodium trifluoromethanesulphinate monohydrate readily distinguishes it from anhydrous sodium trifluoromethanesulphonate which has similar analytical figures. Further distinction is given by their reaction with aqueous sodium hydroxide at 100°: the sulphonate is stable, but the sulphinate evolves fluoroform quantitatively ($CF_3{\cdot}SO_2Na + NaOH \longrightarrow CHF_3 + Na_2SO_3$). Trifluoromethanesulphinic acid is thus the first sulphur compound containing a trifluoromethyl group which liberates fluoroform quantitatively; the others are either stable (*e.g.*, $CF_3{\cdot}S{\cdot}CF_3$) or break down completely (*e.g.*, $CF_3{\cdot}S_2{\cdot}CF_3$, $CF_3{\cdot}SH$). No similar reaction has been observed for alkanesulphinic acids, and trichloromethanesulphinic acid is reported to give the compound $CHCl_2{\cdot}SO_2K$ when heated with aqueous potassium hydroxide (Kolbe, *loc. cit.*; Rathke, *Annalen*, 1872, **161**, 149). Studies on the preparation of trifluoromethanesulphinic acid from its salts will be presented later.

Trifluoromethanesulphenic acid, $CF_3{\cdot}S{\cdot}OH$, was postulated earlier (*J.*, 1952, 2198; 1953, 3219) as an unstable intermediate in the hydrolysis of bistrifluoromethyl disulphide by aqueous base:

$$CF_3{\cdot}S{\cdot}S{\cdot}CF_3 \longrightarrow CF_3{\cdot}S{\cdot}OH + CF_3{\cdot}SH$$

$$\downarrow \qquad\qquad \downarrow$$

$$F^-, CO_3^{--}, S^{--} \qquad F^-, CO_3^{--}, S^{--}$$

and the preparation of its acid chloride, $CF_3{\cdot}SCl$ (*J.*, 1953, 3219), opened up a possible route to it, although all other sulphenic acids are believed to disproportionate ($2R{\cdot}S{\cdot}OH \longrightarrow R{\cdot}SH + R{\cdot}SO_2H$) and have never been isolated. Trifluoromethanesulphenic acid has not been isolated by aqueous hydrolysis of the sulphenyl chloride, but some knowledge of its stability and reactions has been gained.

The hydrolysis of trifluoromethanesulphenyl chloride by water, which is first considered, is more complicated than indicated by the reaction: $CF_3{\cdot}SCl + H_2O \longrightarrow CF_3{\cdot}S{\cdot}OH + HCl$. A large excess of water (*ca.* 40 : 1 molar ratio) causes the yellow colour of the sulphenyl chloride to disappear after a few hours, and bistrifluoromethyl disulphide (55—60% yield in typical experiments) and a small amount (*ca.* 4%) of carbonyl sulphide are formed. The aqueous solution remaining after the hydrolysis contains fluoride ion (5—10%), and when heated with aqueous sodium hydroxide yields fluoroform (33%). The liberation of fluoroform under these conditions reveals the presence of trifluoromethanesulphinic acid and an approximate scheme may thus be written:

$$3CF_3{\cdot}SCl + 2H_2O \longrightarrow CF_3{\cdot}S_2{\cdot}CF_3\ (66{\cdot}7\%) + CF_3{\cdot}SO_2H\ (33{\cdot}3\%) + 3HCl$$

the facts being borne in mind that the yield of the disulphide is not quite that represented by the equation, and that a small amount of carbonyl sulphide and fluoride ion are also formed. Sulphinic acids are often found as hydrolysis products of other sulphenyl halides (Kharasch, Potempa, and Wehrmeister, *Chem. Rev.*, 1946, **39**, 269), and it should be noted in particular that neither trifluoromethanesulphonyl chloride nor trifluoromethanesulphonic acid is a reaction product. Two main reaction schemes are put forward to explain the observed hydrolysis. Both require the initial reaction with water to be represented by :

$$CF_3{\cdot}SCl + H_2O \longrightarrow CF_3{\cdot}SO^- + Cl^- + 2H^+$$

and both require the ion $CF_3{\cdot}SO^-$ (from $CF_3{\cdot}S{\cdot}OH$) to disproportionate rapidly with formation of $CF_3{\cdot}S^-$ (from $CF_3{\cdot}SH$) and $CF_3{\cdot}SO_2^-$ (from $CF_3{\cdot}SO_2H$) :

$$2CF_3{\cdot}SO^- \longrightarrow CF_3{\cdot}S^- + CF_3{\cdot}SO_2^-$$

This is analogous to assumptions made for reactions of other sulphenic acids (Kharasch *et al.*, *loc. cit.*).

Scheme I.

$$2CF_3{\cdot}SCl + 2H_2O \longrightarrow 2CF_3{\cdot}SO^- + 2Cl^- + 4H^+$$
$$2CF_3{\cdot}SO^- \longrightarrow CF_3{\cdot}SO_2^- + CF_3{\cdot}S^-$$
$$CF_3{\cdot}SCl + CF_3S^- \longrightarrow CF_3{\cdot}S{\cdot}S{\cdot}CF_3 + Cl^-$$

Overall reaction :

$$3CF_3{\cdot}SCl + 2H_2O \longrightarrow CF_3{\cdot}SO_2^- \ (33{\cdot}3\%) + CF_3{\cdot}S_2{\cdot}CF_3 \ (66{\cdot}7\%) + 3Cl^- + 4H^+$$

The ion $CF_3{\cdot}S^-$ is known (*J.*, 1953, **3219**, and Part III of this series) to be unstable in water and yields carbonyl sulphide and fluoride; this scheme thus accounts for the formation of fluoride and carbonyl sulphide by breakdown of $CF_3{\cdot}S^-$ competing with its reaction with trifluoromethanesulphenyl chloride, and this is in accord with the yield of bistrifluoromethyl disulphide being less than expected from the overall reaction equation. Neither the disulphide nor trifluoromethanesulphinic acid yields carbonyl sulphide or fluoride in aqueous solution. It was noted earlier that trifluoromethanethiol reacts slowly with trifluoromethanesulphenyl chloride to give the disulphide (*J.*, 1953, **3219**), and it is likely that this reaction is much faster in presence of an ionising solvent.

Scheme II.

$$3CF_3{\cdot}SCl + 3H_2O \longrightarrow 3CF_3{\cdot}SO^- + 3Cl^- + 6H^+$$
$$2CF_3{\cdot}SO^- \longrightarrow CF_3{\cdot}S^- + CF_3{\cdot}SO_2^-$$
$$CF_3{\cdot}SO^- + H_2O \longrightarrow CF_3{\cdot}S^+ + 2OH^-$$
$$CF_3{\cdot}S^+ + CF_3{\cdot}S^- \longrightarrow CF_3{\cdot}S_2{\cdot}CF_3$$

Overall reaction :

$$3CF_3{\cdot}SCl^- + 2H_2O \longrightarrow CF_3{\cdot}SO_2^- + CF_3{\cdot}S_2{\cdot}CF_3 + 3Cl^- + 4H^+$$

This assumes that $CF_3{\cdot}SO^-$ can also react with water to give $CF_3{\cdot}S^+$ at approximately the same rate as it disproportionates, so that $CF_3{\cdot}S^+$ and $CF_3{\cdot}S^-$ ions are formed in equal amounts. The instability of $CF_3{\cdot}S^-$ accounts for the carbonyl sulphide and fluoride ion formation as in Scheme I. The reaction $R{\cdot}SH + R{\cdot}S{\cdot}OH \longrightarrow R_2S_2 + H_2O$ has been postulated to explain disulphide formation in other reactions involving hydrolysis of sulphenyl halides.

It can be predicted from both Scheme I and Scheme II that trifluoromethyl trifluoromethanethiolsulphonate should be formed under suitable conditions :

Scheme I :

$$CF_3{\cdot}SCl + CF_3{\cdot}SO_2^- \longrightarrow CF_3{\cdot}SO_2{\cdot}S{\cdot}CF_3 + Cl^-$$

Scheme II :

$$CF_3{\cdot}S^+ + CF_3{\cdot}SO_2^- \longrightarrow CF_3{\cdot}SO_2{\cdot}S{\cdot}CF_3$$

and this prediction was verified. The concentration of $CF_3 \cdot SO_2^-$ ions was maintained as high as possible by treatment of trifluoromethanesulphenyl chloride with consecutive small amounts of water (molar ratio 1 : 0·4) during several days, and under these conditions the thiolsulphonate, which is stable to water, was isolated with approximately equimolar amounts of the disulphide. Incorporation of the last two equations in Schemes I and II respectively gives :

$$4CF_3 \cdot SCl + 2H_2O \longrightarrow CF_3 \cdot S_2 \cdot CF_3\ (50\%) + CF_3 \cdot SO_2 \cdot S \cdot CF_3\ (50\%) + 4Cl^- + 4H^+$$

for the overall reaction for formation of trifluoromethyl trifluoromethanethiolsulphonate, in good agreement with the experimental yields.

The hydrolysis of trifluoromethanesulphenyl chloride by aqueous sodium hydroxide is next considered. The products depend upon the conditions used : at 70°, fluoride ion (67%), chloride ion (99%), sulphur, and sulphide ion are formed ; at 95°, in addition to the above products in the same yields, fluoroform (33%) is isolated. The scheme :

$$3CF_3 \cdot SCl + 4NaOH \longrightarrow CF_3 \cdot S_2 \cdot CF_3 + CF_3 \cdot SO_2Na + 3NaCl + 2H_2O$$

$$\downarrow \text{NaOH, } 70° \qquad \downarrow \text{NaOH, } 95°$$

$$(66{\cdot}6\%)\ CO_3^{--}, F^-, S^{--}, S \qquad CHF_3\ (33{\cdot}3\%)$$

accounts for this product, since bistrifluoromethyl disulphide is decomposed by aqueous base, whereas the sulphinic acid liberates fluoroform only at 95°. The hydrolysis of other sulphenyl halides has been observed to give disulphide and sulphinic acid in the quantities expected from an equation of the above type (Lecher, Holschneider, Koberle, Spee, and Stocklin, *Ber.*, 1925, **58**, 409 ; Miller and Smiles, *J.*, 1925, 224).

Schemes I and II above thus agree well with the experimental results, and their relation to the aqueous alkaline hydrolysis of bistrifluoromethyl disulphide is next considered. It was postulated earlier that S–S fission occurs, but it is clear that if trifluoromethanesulphenic acid is thus produced it should, according to Scheme I or II, disproportionate to give $CF_3 \cdot S^-$ and $CF_3 \cdot SO_2^-$. Since trifluoromethanesulphinic acid is stable to aqueous alkali at room temperature and at 50°, and liberates fluoroform only at 95°, the alkaline hydrolysis of bistrifluoromethyl disulphide *via* the sulphenic acid should give trifluoromethanesulphinic acid, and this is inconsistent with the quantitative formation of fluoride ion from bistrifluoromethyl disulphide at 50°. It should be noted, however, that Scheme II, when applied to the alkaline hydrolysis, does not necessarily require the actual formation of the disulphide followed by its decomposition, but only that $CF_3 \cdot S^-$ and $CF_3 \cdot S^+$ are unstable in alkaline solution. The instability of the first of these is already known from the reactions of trifluoromethanethiol ($CF_3 \cdot S^- \xrightarrow{OH^-} CO_3^{--}, F^-, S^{--}$) and $CF_3 \cdot S^+$ may well be unstable :

$$CF_3 \cdot S^+ + OH^- \longrightarrow S + CF_3 \cdot OH \xrightarrow{OH^-} CO_3^{--} + F^-$$

This would also account for the formation of free sulphur during the aqueous alkaline hydrolysis of trifluoromethanesulphenyl chloride.

The liberation of free sulphur in the hydrolysis of bistrifluoromethyl disulphide might indicate C–S bond fission instead of S–S fission :

$$OH^- \curvearrowright CF_3 \cdot S \cdot S \cdot CF_3 \longrightarrow CF_3 \cdot OH + CF_3 \cdot S \cdot S^-$$

$$\downarrow \qquad \downarrow$$

$$CO_3^{--}, F^- \qquad CF_3 \cdot S^- + S$$

$$\downarrow$$

$$CO_3^{--}, S^{--}, F^-$$

This fits the experimental observations, would avoid the clash with Scheme I and possibly Scheme II, and also finds support from the hydrolysis of bisheptafluoropropyl disulphide, which can be interpreted in terms of C–S as well as of S–S fission (Part III of this series).

The hydrolysis of trifluoromethyl trifluoromethanethiolsulphonate has also been studied. This ester is stable to water, but decomposed by aqueous alkali, and the products depend upon the conditions: at 50°, fluoride (38%) and sulphide (39%) are formed; at 95°, fluoride (39%), sulphide (99%), and fluoroform (60%) are produced. The appearance of fluoroform at only the higher temperature reveals the formation of trifluoromethanesulphinic acid, formed by S–S bond fission in the thiolsulphonate:

$$CF_3{\cdot}SO_2{\cdot}S{\cdot}CF_3 + OH^- \longrightarrow CF_3{\cdot}SO_2^- + CF_3{\cdot}SO^- + H^+$$

This reaction also produces a sulphenate ion which has already been postulated to disproportionate readily. Scheme II can thus be applied to the reaction:

$$3CF_3{\cdot}SO_2{\cdot}S{\cdot}CF_3 + 3OH^- \longrightarrow 3CF_3{\cdot}SO_2^- + 3CF_3{\cdot}SO^- + 3H^+$$

$$2CF_3{\cdot}SO^- \longrightarrow CF_3{\cdot}S^- + CF_3{\cdot}SO_2^-$$

$$CF_3{\cdot}SO^- + H_2O \longrightarrow CF_3{\cdot}S^+ + 2OH^-$$

$$CF_3{\cdot}S^- + CF_3{\cdot}S^+ \longrightarrow CF_3{\cdot}S_2{\cdot}CF_3$$

Overall reaction:

$$3CF_3{\cdot}SO_2{\cdot}S{\cdot}CF_3 + 3OH^- \longrightarrow (CF_3)_2S_2 + 4CF_3{\cdot}SO_2^- + H^+ + H_2O$$

$$\downarrow \text{NaOH } 50° \qquad \downarrow \text{NaOH } 95°$$

$$(33{\cdot}3\%)\ CO_3^{--},\ F^-,\ S^{--},\ S \qquad CF_3H\ (66{\cdot}7\%)$$

The figures, 33·3% of fluoride and 66·7% of fluoroform at 95°, are close to the experimental values. Here again, the scheme does not necessarily require the intermediate formation of the disulphide, but only that $CF_3{\cdot}S^-$ and $CF_3{\cdot}S^+$ are unstable as suggested previously. The equation $3R{\cdot}SO_2{\cdot}SR + 4NaOH \longrightarrow R_2S_2 + 4R{\cdot}SO_2Na + 2H_2O$ is analogous to that proposed for hydrolysis of other thiolsulphonates (Otto and Rössing, *Ber.*, 1886, **19**, 1235).

Scheme I can be applied to the hydrolysis of the thiolsulphonate only if the reaction

$$CF_3{\cdot}S^- + CF_3{\cdot}SO_2{\cdot}S{\cdot}CF_3 \longrightarrow CF_3{\cdot}SO_2^- + CF_3{\cdot}S_2{\cdot}CF_3$$

is possible. Thus, although two reaction schemes can be proposed to explain the hydrolysis of trifluoromethanesulphenyl chloride, Scheme II is preferred, since it is in reasonable agreement with the observed hydrolysis of trifluoromethyl trifluoromethanethiolsulphonate. The hydrolysis of bistrifluoromethyl disulphide is not completely compatible with either Scheme I or II unless C–S bond fission occurs in preference to S–S bond fission.

The structure of trifluoromethyl trifluoromethanethiolsulphonate isolated from the controlled hydrolysis of trifluoromethanesulphenyl chloride follows from its synthesis by interaction of zinc trifluoromethanesulphinate and trifluoromethanesulphenyl chloride:

$$(CF_3{\cdot}SO_2)_2Zn + 2CF_3{\cdot}SCl \longrightarrow 2CF_3{\cdot}SO_2{\cdot}S{\cdot}CF_3 + ZnCl_2$$

Attempts to synthesise it by interaction of trifluoromethanesulphonyl chloride and trifluoromethanethiol failed. The compounds $R_2S_2O_2$ have only recently been shown to be thiolsulphonates $R{\cdot}SO_2{\cdot}SR$, and not disulphoxides $R{\cdot}SO{\cdot}SO{\cdot}R$ (Zincke and Farr, *Annalen*, 1912, **391**, 57; Child and Smiles, *J.*, 1926, 2696; Gibson, Miller, and Smiles, *J.*, 1925, 1821; Cymerman and Willis, *J.*, 1951, 1332). The infrared spectrum of trifluoromethyl trifluoromethanethiolsulphonate also reveals the $-SO_2-$ group as shown in the Table where it is compared with related compounds. The $-SO_2-$ groups in sulphuryl chloride, trifluoromethanesulphonyl chloride, and trifluoromethyl trifluoromethanethiolsulphonate do not show specific absorption in the ultraviolet region.

Infrared Spectra.—The $-SO_2-$ group in sulphonyl or sulphuryl halides gives rise to

symmetric (st.-a.) and asymmetric (st.-s.) stretching vibrations, as does the $-NO_2$ group in *C*-, *O*-, or *N*-nitro-compounds. Increase in electronegativity of the group R in $R{\cdot}SO_2Cl$ causes a progresive decrease in the wavelength of the st.-a. vibration in the series $R = CH_3$,

Infrared absorption bands (μ) of compounds containing $-SO_2-$ or $>SO$ groups.

Compound		C.S. No.*	Asymmetric stretching	Symmetric stretching	Compound		C.S. No.*	Asymmetric stretching	Symmetric stretching
				Acid halides.					
SO_2F_2 [a]	(v)	—	6·66	7·88	SO_2 [e]	(v)	—	7·65	8·65
$CF_3{\cdot}SO_2Cl$ [b]	(v)	218	6·95	8·07 or 8·90	$(C_6H_{11})_2SO_2$	(s)	—	7·62	8·85
SO_2Cl_2 [b]	(v)	219	6·96	8·30	Ph_2SO_2 [f]	(N)	223	7·59, 7·65 7·73 (t)	8·65
$CH_3{\cdot}SO_2F$ [c]	(v)	—	6·90, 6·97 (d)	8·20	,,	(S)	—	7·48	8·59
$CCl_3{\cdot}SO_2Cl$	(N)	220	7·12	8·45	$(Ph{\cdot}SO_2)_2S$ [b]	(N)	—	7·35, 7·44 (d)	8·58
,,	(S)	—	7·11	8·42					
,,	(v)	—	7·04	8·35					
$CH_2{\cdot}SO_2Cl$	(l) [b,d]	—	7·33	8·53					
,,	(v) [b]	221	7·15	8·42					
,,	(S) [b]	—	7·25	8·51					
				Thiolsulphonates, $R{\cdot}SO_2{\cdot}SR$.					
R					R				
CF_3 [b]	(v)	222	7·03	8·10 or 9·10	*p*-$C_6H_4{\cdot}CO{\cdot}NH_2$ [b]	(N)	—	7·45	8·67
p-$C_6H_4{\cdot}CN$ [b]	(N)	—	7·45	8·67	Ph [b]	(N)	—	7·51	8·75
				Sulphonates, [g] $R{\cdot}SO_3^-$.					
$CF_3{\cdot}SO_3Na$	(N)	137	7·82	9·60	$CH_3{\cdot}SO_3Na$	(N)	136	8·37	9·50
$(CF_3{\cdot}SO_3)_2Ba$	(N)	139	7·85	9·62	$CH_3{\cdot}SO_3H$	(l)	135	8·4	9·44
$CF_3{\cdot}SO_3Ag$	(N)	138	7·9	9·75	—	—	—	—	—

Compound		C.S. No.*	S:O vibration	Compound		S:O vibration
			Thionyl halides, sulphoxides, sulphites.			
SOF_2 [b]	(v)	—	7·49, 7·55 (d)	$(C_6H_{11})(CH_3)SO$ [f]	(S)	9·48
$SOCl_2$ [f]	(v)	224	7·96, 8·03 (d)	Ph·SOMe [f]	(S)	9·48
$(MeO)_2SO$ [b]	(l)	—	8·33	Ph_2SO [f]	(S)	9·48
$(EtO)_2SO$ [b]	(l)	—	8·33	,,	(N) [b]	9·60
—	—	—	—	Bu^t_2SO [b]	(S)	9·62
—	—	—	—	,,	(N) [b]	9·82
			Sulphinates, RSO_2^-.			
$CF_3{\cdot}SO_2Na$ [b]	(N)	225	9·9 (?)	$Ph{\cdot}SO_2Na$ [b]	(N)	9·8
$(CF_3{\cdot}SO_2)_2Zn$ [b]	(N)	226	9·8 (?)	—	—	—

t = triplet, d = doublet, v = vapour, l = liquid, N = Nujol mull, S = solution in CCl_4.

[a] Perkins and Wilson, *J. Chem. Phys.*, 1952, **20**, 1791. [b] Present work. [c] T. Gramstad, unpublished results; the liquid has corresponding peaks at 7·20 and 8·30 μ. Ham and Hambly (*Austral. J. Chem.*, 1953, **6**, 33) record bands at 7·16 and 8·26 μ in the infrared and 7·14 and 8·26 μ for the Raman spectrum which can be assigned to the SO_2 vibration. [d] T. Gramstad, unpublished results. Ham and Hambly (*loc. cit.*) record bands at 7·31 and 8·51 μ (infrared) and 7·35 and 8·56 μ (Raman) which can be assigned to the SO_2 vibration. [e] Herzberg, "Infrared and Raman Spectra," Van Nostrand, New York, 1947, p. 285. [f] C_6H_{11} = *cyclo*hexyl; Barnard, Fabian, and Koch, *J.*, 1949, 2442; Schreiber (*Analyt. Chem.*, 1949, **21**, 1168) has also examined the spectra of sulphones. [g] Present work; Cymerman and Willis (*loc. cit.*) report 7·58, 7·62, 7·70, and 8·63 μ. [h] Cymerman and Willis, *loc. cit.* [i] Haszeldine and Kidd, *J.*, 1954, 4228. [j] Schreiber (*loc. cit.*) reports 8·08 μ; Cabannes and Rousset (*Ann. Physique*, 1933, **19**, 229) report 8·14 μ (Raman). [k] Matossi and Aderhold, *Z. Physik*, 1931, **68**, 683.

* Spectra bearing C.S. Nos. have been deposited with the Chemical Society. Copies, price 3*s.* 0*d.* each per copy, may be obtained on application, quoting the C.S. No., to the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

CCl_3, Cl, and CF_3 (Table); the st.-s. vibration also decreases in this series provided that 8·07 is taken as this vibration for trifluoromethanesulphonyl chloride. The spectrum of the last compound shows two strong bands, at 8·07 and 8·90 μ, either of which could be

assigned to the st.-s. vibration, and the other to a C–F stretching vibration. The assignment for methanesulphonyl chloride is not open to doubt, since the 7·33 and 8·53 μ bands are the strongest in the spectrum; the assignment for trichloromethanesulphonyl chloride is particularly clear, since there are no C–H vibrations to cause confusion.

In favour of the assignment of the 8·07 μ band to the st.-s. vibration in trifluoromethanesulphonyl chloride are the following points: (*a*) The shift to shorter wavelength for the st.-s. vibration on change of R in $R{\cdot}SO_2Cl$ from CH_3 to CCl_3 indicates an increase in the contribution of $>S{:}O$ relative to that of $>\overset{+}{S}–O^-$ with increase in inductive effect of R; further shift to shorter wavelength is to be expected when $R = CF_3$. The spectra of methane- and trichloromethane-sulphonyl chloride must be compared for the compounds in similar physical states, in this case as vapours or as solutions in carbon tetrachloride. The spectra of methane- and trifluoromethane-sulphonyl chloride as vapours must similarly be compared to observe the trend. (*b*) Shift to shorter wavelength for the st.-s. vibration also occurs in the series $R{\cdot}SO_2F$ where $R = CH_3$ or F (Table).

In favour of the 8·90 μ band for the st.-s. vibration are the following points: (*a*) Analogy with *C*-nitro-compounds, where it has been shown (*J.*, 1953, 2525) that although the st.-a. band moves to shorter wavelength with increase in negativity of R in $R{\cdot}NO_2$, the st.-s. band moves to longer wavelength. (*b*) Trifluoromethanesulphonyl fluoride shows bands at 6·77 μ (st.-a.) and at 8·07 and 8·69 μ (T. Gramstad, unpublished results). The 8·07 μ band is at the same position as for trifluoromethanesulphonyl chloride, and could plausibly be assigned to a C–F vibration; the 8·69 μ band is shifted relative to the corresponding band (8·90 μ) in trifluoromethanesulphonyl chloride and this could be attributed to the effect on the st.-s. $–SO_2–$ vibration of increase in electronegativity on replacement of chlorine by fluorine.

The spectra of sulphuryl chloride and fluoride, however, also reveal an unambiguous shift of the st.-s. vibration to shorter wavelength, and the assignment of the 8·07 μ band to this vibration for trifluoromethanesulphonyl chloride is thus preferred, particularly when the difference in wavelength (1·0—1·3 μ) between the st.-a. and st.-s. wavelengths is also considered. The sulphones shown in the Table resemble sulphur dioxide, and their st.-a. and st.-s. vibrations lie at longer wavelengths than those of the acid halides. There is thus a shift to shorter wavelength of these vibrations in the series $R{\cdot}SO_2X$ with $X = C_{aliph.} > C_{arom.} > S > Cl > F$.

The spectrum of trifluoromethyl trifluoromethanethiolsulphonate shows a marked resemblance to that of trifluoromethanesulphonyl chloride, with strong bands at 7·03, 8·10, and 9·10 μ. Following the assignments for the chloro-compound, the first of these is assigned to the st.-a. vibration, and the second is given preference over the third for the st.-s. vibration. The $S{:}O$ vibration in a disulphoxide structure $CF_3{\cdot}SO{\cdot}SO{\cdot}CF_3$ for the compound $CF_3{\cdot}S_2O_2{\cdot}CF_3$ would not be at shorter wavelength than that in thionyl fluoride (7·5 μ; Table), where R in R·SO·R has maximum electronegativity, and would probably lie between 8 and 9 μ; with this structure the 7·03 μ band could not be assigned. The similarity to trifluoromethanesulphonyl chloride and the intensity and position of the 7·03 μ band in the spectrum of $CF_3{\cdot}S_2O_2{\cdot}CF_3$ clearly lead to the thiolsulphonate structure which is in accord with the structure determined by synthesis. Distinct shifts to shorter wavelength of the $–SO_2–$ bands with increase in inductive effect of R in $R{\cdot}SO_2{\cdot}SR$ are apparent.

The $–SO_2–$ vibrations in metal sulphonates are moved to longer wavelength relative to those in sulphones, thiolsulphonates, and sulphonyl halides, just as the $C{:}O$ vibration of carboxylic acids is moved to longer wavelength in the salt. The assignment of the st.-a. vibration is clear, whereas that of the st.-s. vibration is less certain. When R in $R{\cdot}SO_3^-$ is CF_3 there is the expected shift to shorter wavelength for the st.-a. band (Table), but either the st.-s. band moves to longer wavelength or it must be assigned to other than the strong band near 9·6 μ, presumably to a band in the C–F stretching vibration region (8—9 μ).

The $S{:}O$ stretching vibration in a sulphoxide is at 9·5 μ, and attachment of the negative oxygen atoms to sulphur as in a dialkyl sulphite causes a marked shift (1·2 μ) to shorter wavelength (Table). This trend is continued for thionyl chloride and fluoride (Table) and

the S:O group is more sensitive than the $-SO_2-$ group in this respect. Clear predictions can thus be made for the position of the S:O vibration in R·SO·OMe (8·7—9·1 μ), R·SOCl (8·5—8·9 μ), and R·SOF (8·2—8·8 μ) where R = alkyl or aryl, with shifts of 0·3—0·5 μ to shorter wavelength when R = perfluoroalkyl.

The sulphinates listed in the Table show a strong band at 9·8 μ which is plausibly assigned to the $R·SO_2^-$ vibration, but this must be regarded as tentative and may need modification as more examples become available.

Experimental

Bistrifluoromethyl disulphide, trifluoromethanesulphenyl chloride, and trifluoromethanesulphonic acid were prepared as described earlier (*J.*, 1953, 3219; 1954, 4228).

Trifluoromethanesulphonyl Chloride.—(a) *From trifluoromethanesulphonic acid.* The acid (0·714 g.) and phosphorus pentachloride (2·45 g.), heated at 100° (4 hr.) in a 30-ml. Pyrex tube, gave volatile products which were distilled *in vacuo* and identified as phosphorus oxychloride (0·542 g.), b. p. 106°, hydrogen chloride (0·176 g., 98%) (Found: *M*, 37. Calc. for HCl: *M*, 36·5), and *trifluoromethanesulphonyl chloride* (0·504 g., 63%), b. p. 31·6° (isoteniscope) (Found: Cl, 21·2%; *M*, 169. CO_2ClF_3S requires Cl, 21·1%; *M*, 168·5). The sulphonyl chloride freezes to a white solid which sublimes in a high vacuum.

(b) *From trifluoromethanesulphenyl chloride.* Three typical reactions show how the products vary with the relative quantities of reactants taken.

(i) Trifluoromethanesulphenyl chloride (3·70 g., 0·0271 mole), chlorine (5·00 g., 0·0715 mole), and water (5·00 g., 0·278 mole) were vigorously shaken in a 50-ml. Pyrex tube for 7 days, to give trifluoromethanesulphonyl chloride (4·47 g., 98%), b. p. 31·6° (Found: Cl, 21·2%; *M*, 169), and gaseous hydrogen chloride (0·528 g.). The sulphonyl chloride was shown to be identical with the compound prepared from trifluoromethanesulphonic acid by comparison of infrared spectra.

(ii) Trifluoromethanesulphenyl chloride (2·333 g., 0·017 mole), chlorine (1·17 g., 0·0165 mole), and water (4·00 g., 0·222 mole) were vigorously shaken in a 30-ml. Pyrex tube (48 hr.), to give a colourless lower layer. The volatile products were distilled *in vacuo*, to give hydrogen chloride (0·142 g.) and a mixture (1·970 g.; *M*, 177·3), analysed by infrared spectroscopy, of bistrifluoromethyl disulphide (36% yield) and trifluoromethanesulphonyl chloride (47% yield).

(iii) Vigorous shaking of a mixture of trifluoromethanesulphenyl chloride (0·9857 g., 0·0072 mole), chlorine (0·2811 g., 0·0040 mole), and water (3·00 g., 0·167 mole) in a sealed tube caused disappearance of the yellow colour in 2 hr. After 24 hr., distillation gave gaseous hydrogen chloride and a mixture (0·5010 g.; *M*, 184·7) of bistrifluoromethyl disulphide (37% yield) and trifluoromethanesulphonyl chloride (20% yield), analysed by infrared spectroscopy.

A control experiment showed that bistrifluoromethyl disulphide was recovered quantitatively after treatment with chlorine and water at room temperature.

(c) *From oxidation of trifluoromethanesulphenyl chloride by hydrogen peroxide.* The sulphenyl chloride (2·75 g.) was condensed into a 50-ml. flask and 35% hydrogen peroxide (20 ml.) was added carefully. The flask was allowed to warm to room temperature so that the sulphenyl chloride was under reflux (condenser at −78°); the rate of reflux decreased as reaction occurred. After a final heating at 50° for 2 hr. the liquid was colourless. Products more volatile than water were transferred to a gas-manipulation apparatus and distilled *in vacuo* to give a mixture (2·076 g.; *M*, 179·2) shown by infrared spectroscopic analysis to consist of bistrifluoromethyl disulphide (35% yield) and trifluoromethanesulphonyl chloride (40% yield). Examination of the aqueous solution revealed the presence of fluoride (11%) and trifluoromethanesulphonic acid (7%; isolated as its barium salt and identified by means of its infrared spectrum), but no trifluoromethanesulphinic acid.

Hydrolysis of Trifluoromethanesulphonyl Chloride.—Trifluoromethanesulphonyl chloride (0·151 g.) was present as an immiscible layer after being kept with water (1·5 ml.) in a sealed tube at 25° for 4 days. Less than 5% hydrolysis had occurred. Hydrolysis was complete and quantitative after 12 hr. at 75°, and not even traces of fluoride were detected. Quantitative hydrolysis without liberation of fluoride similarly occurred with 15% aqueous sodium hydroxide at 25° (12 hr.). Trifluoromethanesulphonic acid was identified by means of the infrared spectrum of its sodium salt.

Trifluoromethanesulphinic Acid.—(a) *As sodium salt.* Trifluoromethanesulphonyl chloride (1·384 g.), zinc dust (3·0 g.), and water (4·0 ml.) were kept 4 days at 25° in a sealed 30-ml. Pyrex tube. The sulphonyl chloride slowly disappeared, and no volatile products were produced.

The aqueous solution was filtered and the zinc precipitated with " AnalaR " sodium carbonate; filtration followed by freeze-drying gave a white deliquescent solid which was extracted with acetone. The extract was evaporated to dryness at room temperature *in vacuo*, then dried to constant weight at 45° *in vacuo*, to give *sodium trifluoromethanesulphinate monohydrate* (0·551 g., 38%) (Found : CF_3, 39·5; Na, 13·2. $CF_3{\cdot}SO_2Na,H_2O$ requires CF_3, 39·6; Na, 13·2). The salt was analysed for CF_3 by heating a sample (0·2161 g.) with 15% aqueous sodium hydroxide (5 ml.) at 95° (12 hr.) in a sealed tube; the fluoroform evolved (0·0866 g., 99·8%) (*M*, 70) was identified spectroscopically. Fluoride was not liberated. Sodium was determined as sodium sulphate by treatment of the salt with concentrated sulphuric acid in the usual manner.

(b) *As zinc salt.* Trifluoromethanesulphonyl chloride (0·920 g.), zinc dust (2·5 g.), and water (3 ml.) were allowed to react as above. The aqueous solution was filtered and evaporated to dryness at room temperature *in vacuo*. The residue was extracted with anhydrous ether to remove zinc chloride and the insoluble material was centrifuged three times with more ether. The residual white hygroscopic solid was dried over phosphoric anhydride and shown to be almost pure hydrated zinc trifluoromethanesulphinate (0·3244 g., 15%) [Found : CF_3, 35·1. Calc. for $(CF_3{\cdot}SO_2)_2Zn,3H_2O$: CF_3, 35·9. Calc. for $(CF_3SO_2)_2Zn,4H_2O$: CF_3, 34·2%]. It was found difficult to repeat this experiment, since separation of zinc chloride by ether-extraction is difficult and tedious.

It should be noted that the yields given above are minimum yields, since if the zinc or sodium salts are not actually isolated a quantitative yield of fluoroform can be obtained by treatment of the aqueous solution with base, showing that trifluoromethanesulphinic acid formation is quantitative. Thus, when trifluoromethanesulphonyl chloride (0·3393 g.) was treated with zinc dust (0·5 g.) and water (3 ml.) as above, and the filtered aqueous solution was heated with sodium hydroxide (1 g.) at 95° (12 hr.), fluoroform (0·1395 g., 99%) (*M*, 70), but no fluoride, was produced.

Hydrolysis of Trifluoromethanesulphenyl Chloride.—(a) *With a large excess of water.* The sulphenyl chloride (1·533 g.) and water (8·0 ml.) were vigorously shaken in a 30-ml. Pyrex tube at room temperature. The yellow colour of the sulphenyl compound disappeared after 3 hr., and shaking was continued for a further 9 hr. The volatile products were distilled *in vacuo*, to give bistrifluoromethyl disulphide (0·647 g., 57%) (*M*, 202), identified spectroscopically, and a more volatile fraction (0·023 g.) (Found : *M*, 60), shown by infrared spectroscopy to be carbonyl sulphide (Calc. for COS : *M*, 60). The aqueous solution was made alkaline with sodium hydroxide and heated at 95° for 12 hr. to give fluoroform (0·258 g., 33%) (*M*, 70) as the only volatile product. The fluoride content of the remaining alkaline solution was equivalent to 6·0% of the trifluoromethanesulphenyl chloride.

In further experiments the yield of the disulphide varied from 55% to 60%, and the fluoride ion from 5% to 10%. The aqueous solution always gave fluoroform in 33% yield on treatment with aqueous base at 95°.

(b) *With small amounts of water.* Trifluoromethanesulphenyl chloride (2·051 g., 0·0150 mole) was treated with successive small portions of water (each *ca.* 0·100 g., 0·0056 mole) at 12—24 hr. intervals in a Pyrex tube at room temperature. When 0·47 g. of water had been added the yellow colour of the sulphenyl halide began to fade and the aqueous globules had a deep yellow colour. When a total of 1·17 g. of water had been added the organic layer was colourless and the aqueous layer deep yellow. Distillation of the volatile products *in vacuo* gave trifluoromethyl trifluoromethanethiolsulphonate (0·206 g., 15%) (Found : *M*, 234. Calc. for $C_2O_3F_6S_2$: *M*, 234), b. p. 69—70° (micro), n_D^{17} 1·3480, spectroscopically identical with the compound synthesised from zinc trifluoromethanesulphinate as described below. A fraction (1·175 g.) (*M*, 212·5) was also isolated and shown to consist of bistrifluoromethyl disulphide (49%) and trifluoromethyl trifluoromethanethiolsulphonate (27%) by spectroscopic analysis. The aqueous solution contained 1% of fluoride ion. The total yield of trifluoromethyl trifluoromethanethiolsulphonate is thus 42%.

(c) *With aqueous sodium hydroxide.* Two typical experiments are given to illustrate the temperature dependence.

(i) Trifluoromethanesulphenyl chloride (0·1516 g.) was heated at 60° with 15% aqueous sodium hydroxide (5 ml.) in a Pyrex tube for 12 hr. A yellow solid (sulphur) formed even at room temperature but dissolved on heating to give a yellow solution. No volatile products were formed, and the aqueous solution contained fluoride (67·0%) and chloride (99·1%), yields being based on the sulphenyl chloride.

(ii) Reaction of trifluoromethanesulphenyl chloride (0·3136 g.) with 15% aqueous sodium hydroxide (8 ml.) rapidly gave a yellow solution with deposition of sulphur. After being

heated at 95° (12 hr.) the solution was dark green, and contained fluoride (66·2% based on CF_3·SCl). The volatile product was fluoroform (0·0526 g., 33·2%) (*M*, 70), identified spectroscopically.

Synthesis of Trifluoromethyl Trifluoromethanethiolsulphonate.—Trifluoromethanesulphenyl chloride (2·110 g.) was converted into zinc trifluoromethanesulphinate as described previously; the filtered aqueous solution was evaporated to dryness and the residual solid was dried at 10^{-4} mm. for 24 hr. Reaction of the solid with trifluoromethanesulphenyl chloride (0·555 g.) gave (5 days) the *trifluoromethanethiolsulphonate* (0·641 g., 67% based on CF_3·SCl), b. p. 69—70°, n_D^{15} 1·3480 (Found: F, 48·0; S, 27·3%; *M*, 234. $C_2F_6O_2S_2$ requires F, 48·7; S, 27·4%; *M*, 234). No other volatile products were formed; some loss of the thiolsulphonate occurred, since it was adsorbed on the solid residue, and could be removed *in vacuo* only with difficulty.

Trifluoromethyl trifluoromethanethiolsulphonate was not formed when trifluoromethanethiol (0·0933 g.) and trifluoromethanesulphonyl chloride (0·1648 g.) were kept in a sealed tube for 5 days.

Bis(trifluoromethylthio)mercury (0·322 g.) dissolved in, but did not react with, trifluoromethanesulphonyl chloride (0·088 g.) at room temperature. Reaction occurred at 55° (3 days) but the products obtained were produced by decomposition of the mercurial and did not contain trifluoromethyl trifluoromethanethiolsulphonate. Thirty-three per cent. of the mercurial was recovered.

Hydrolysis of Trifluoromethyl Trifluoromethanethiolsulphonate.—This compound is stable to water but hydrolysed by aqueous sodium hydroxide. The annexed Table summarises reactions carried out with 15% aqueous sodium hydroxide in sealed Pyrex tubes for 12 hr. at the temperature shown. The fluoride and sulphide (including polysulphide and free sulphur) present in the resulting aqueous solution were determined in the usual manner, and the fluoroform was characterised by b. p., molecular weight, and infrared spectroscopy.

Temp.	CHF_3 (%)	F^- (%)	S^{--} (%)	Temp.	CHF_3 (%)	F^- (%)	S^{--} (%)
50°	—	38	39	95°	60·3	39·6	99·6
75	34·2	33·9	68	95	59·3	39·7	99·5

Spectra.—A Perkin-Elmer Model 21 Spectrophotometer with rock-salt optics was used for the infrared spectra. The thionyl fluoride was an analytically pure sample (*J.*, 1953, 3219); thionyl and sulphuryl chlorides were redistilled commercial samples. A 10-cm. gas cell was used for the majority of the vapour spectra. Solids were examined as mulls in Nujol and hexachlorobutadiene, and solutions were in carbon tetrachloride. Sodium and zinc trifluoromethanesulphinates are hydrated and show bands caused by water at 3 and 6 μ.

CF_3·SO_2Cl (vapour)	λ 240	230	220	210
	ε 3	15	45	130
CF_3·SO_2·S·CF_3 (vapour)	λ 260	250	240	230
	ε 13	21	32	41
SO_2Cl_2 (vapour)	λ 250	240	230	—
	ε 98	190	280	—

The ultraviolet spectra given in the annexed Table were determined with a Unicam Spectrophotometer.

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*Pyrone Series. Part II.** 4 : 5 : 6-*Triaryl-2-pyrones.*

By Gabra Soliman and Ibrahim El-Sayed El-Kholy.

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Condensation of deoxybenzoins with ethyl phenylpropiolate leads to *cis*- and *trans*-β-desylcinnamic esters of which the former subsequently cyclise to triaryl-2-pyrones (IV). *cis*-β-Desylcinnamic acids (V) and substituted vinylacetic acids (VI) are obtained by alkaline fission of the pyrones. Conversely, the esters of these acids give the pyrones under the influence of basic reagents. *trans*-β-Desylcinnamic esters (III) undergo an acid-catalysed change to the esters of substituted vinylacetic acids.

cis-β-Desylcinnamic acids are readily decarboxylated to the ketones (IX*b*) when heated.

The mechanisms proposed for the syntheses of aryl-2-pyrones from acetylenic esters (Ruhemann, *J.*, 1910, **457**) or acetylenic ketones (Kohler, *J. Amer. Chem. Soc.*, 1922, **44**, 379; Sistaré, Vila, and Escala, *Anales Fis. Quim.*, 1952, **48**, *B*, 593) involve elimination of alcohol from the intermediate Michael addition products. Hitherto, our knowledge regarding the nature of such intermediate keto-esters has been rather scanty. Recently, however, Walker (*J. Amer. Chem. Soc.*, 1954, **76**, 309) prepared two Michael adducts from 2 : 3-dimethoxyphenylpropiolic acid derivatives and acetylacetone, though he failed to isolate analogous adducts with ethyl acetoacetate. Though we believe that the failure to obtain such intermediate unsaturated keto-esters is due to inadequate control of the condensation, there is a complication that the esters should exist in *cis*- and *trans*-forms, of which the former are liable to cyclise.

We found that condensation of deoxybenzoin with ethyl phenylpropiolate in presence of sodium ethoxide proceeds to completion, and 4 : 5 : 6-triphenyl-2-pyrone was accompanied by a compound $C_{25}H_{22}O_3$ whose properties showed it to be ethyl *trans*-β-desylcinnamate (III; R = H). On the other hand, alkaline fission of 4 : 5 : 6-triphenyl-2-pyrone yielded a mixture of *cis*-β-desylcinnamic acid (V; R = H) and 5-oxo-3 : 4 : 5-triphenylpent-3-enoic acid (VI; R = H), whose esters were readily converted into the pyrone by sodium ethoxide or traces of alcoholic alkali. Moreover, the methyl pentenoate (VIII; R = H) was prepared by the action of traces of hydrochloric acid on ethyl *trans*-β-desylcinnamate in methanol.

The behaviour of the methyl pentenoate (VIII; R = H) towards basic reagents suggests that it is not merely a methanolysis product. Further, its non-identity with methyl *cis*-β-desylcinnamate excludes its formation by an acid-catalysed *trans*–*cis*-change. Thus, it is the outcome of a shift in the position of the double bond. The presence of the group O:C·CH·C:C·C:O in β-desylcinnamic acid accounts for the mobility of the double bond and explains the ease of pyrone formation from *cis*-β-desylcinnamic esters as well as from the methyl pentenoate (VIII; R = H). The existence of the acid (VI; R = H) among the hydrolysis products of the pyrone is attributable to the same reason.

Irrespective of the configuration of the pent-3-enoate (VIII; R = H), a base-catalysed change in the position of the double bond should lead to a mixture of *cis*- and *trans*-β-desylcinnamic esters of which the latter does not cyclise. Under carefully controlled conditions, however, we have been unable to find such a *trans*-ester alongside the pyrone.

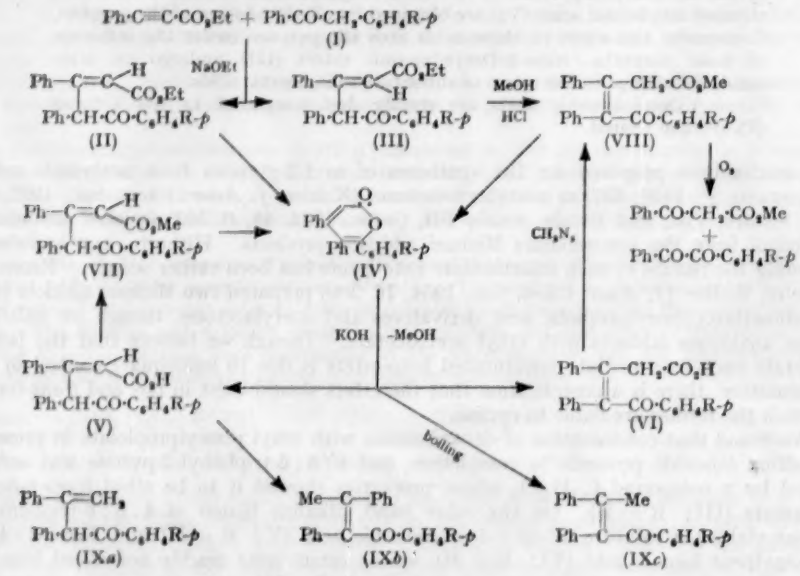
Unlike methyl β-benzoyl-α-phenylcrotonate (Kohler and Barrett, *J. Amer. Chem. Soc.*, 1924, **46**, 747), methyl *cis*-β-desylcinnamate and methyl 5-oxo-3 : 4 : 5-triphenylpent-3-enoate are equally stable towards acidic reagents. So differentiation between the two isomers is possible only by physical methods or ozonolysis.

On account of the presence of an enolising centre next to the asymmetric carbon atom in β-desylcinnamic esters, they are liable to racemisation by alkali. Nevertheless, ethyl *trans*-β-desylcinnamate and methyl *cis*-β-desylcinnamate are dextrorotatory whereas

* Part I, *J.*, 1954, 1755.

methyl 5-oxo-3 : 4 : 5-triphenylpent-3-enoate is optically inactive. Apparently, the activity of the former esters is due to partial resolution during purification.

Ozonolysis of methyl 5-oxo-3 : 4 : 5-triphenylpent-3-enoate (VIII; R = H) led to benzil and benzoylacetic ester which was detected by the ferric chloride reaction and by hydrolysis to acetophenone. On the other hand, methyl *cis*-β-desylcinnamate gave on ozonolysis oxalic acid, benzil, and benzoic acid, but dibenzoylphenylmethane (Marshall, *J.*, 1915, 520) could not be detected among the resinous products which predominated.



The mechanism proposed for the synthesis of 4 : 5 : 6-triphenyl-2-pyrone is equally applicable to 6-*p*-methoxyphenyl-4 : 5-diphenyl-2-pyrone (IV; R = OMe) and 5 : 6-di-*p*-methoxyphenyl-4-phenyl-2-pyrone. They were obtained alongside ethyl *trans*-β-4-methoxydesylcinnamate (III; R = OMe) and ethyl *trans*-β-4 : 4′-dimethoxydesylcinnamate, respectively, from 4-methoxydeoxybenzoin and 4 : 4′-dimethoxydeoxybenzoin.

Analogously to ethyl *trans*-β-desylcinnamate, the *trans*-ester (III; R = OMe) is converted into the ester (VIII; R = OMe) on methanolysis. And alkaline fission of the pyrone (IV; R = OMe) led to a mixture of *cis*-β-4-methoxydesylcinnamic acid (V; R = OMe) and the acid (VI; R = OMe). Conversely, the pyrone was obtained from the esters of these two acids by basic reagents.

Condensation of *meso*-*C*-methyldeoxybenzoin with ethyl phenylpropiolate gave an oil from which a crystalline ester $C_{26}H_{24}O_2$ was obtained and shown to be a Michael adduct. However, *meso*-*C*-phenyldeoxybenzoin failed to react.

A neutral compound has been obtained by pyrolysis of *cis*-β-desylcinnamic and 5-oxo-3 : 4 : 5-triphenylpent-3-enoic acid. Among the three structural formulæ which are consistent with its analysis, the formula (IX*b*; R = H) is assigned to it by elimination of the two other possibilities : it is not identical with Ruhemann's ketone (*loc. cit.*) whose structure (IX*c*; R = H) was established by oxidation to acetophenone and benzoic acid; and a substance of the structure (IX*a*; R = H) should give an oxime and formaldehyde on ozonolysis, whereas the new ketone is inert towards carbonyl reagents and gave on ozonolysis acetophenone and benzil. Thus it is stereoisomeric with Ruhemann's ketone, and being the higher-melting form would be the *trans*-isomer (IX*b*). Again, formation of

this ketone appears to involve a shift in the position of the double bond during decarboxylation. Likewise, the ketone (IX*b*; R = OMe) was obtained by heating *cis*-β-4-methoxydesylcinnamic acid.

The crystalline compounds obtained by heating the thermolabile *trans*-desyl esters (III; R = H and OMe) are being studied in order to gain additional information regarding their configuration.

Experimental

Light petroleum used had b. p. 60—80°, unless otherwise stated.

Condensation of Deoxybenzoin with Ethyl Phenylpropiolate.—Deoxybenzoin (5·6 g., 1 mol.) and ethyl phenylpropiolate (5 g., 1 mole) were successively added to an ice-cold ethereal suspension of sodium ethoxide (1·95 g., 1 mol.), and the mixture was kept in the ice-chest for 2 days. It was then poured into water and the precipitated 4 : 5 : 6-triphenyl-2-pyrone (4 g.) was separated from the ethereal and the alkaline layers. The ethereal solution yielded an oily residue (1·6 g.) from which 0·5 g. of the pyrone were recovered. The alkaline layer was acidified and extracted with ether, and the solution was shaken with sodium hydrogen carbonate which was then acidified and extracted with ether. 4 : 5 : 6-Triphenyl-2-pyrone crystallised from acetic acid in pale yellowish prismatic needles, m. p. 246° (Found : C, 85·1; H, 5·2. Calc. for $C_{23}H_{16}O_2$: C, 85·2; H, 5·0%).

Ethyl trans-β-*desylcinnamate* was isolated from the viscous residue (3·5 g.) recovered from the non-acidic ethereal extract. It solidified on cooling, crystallised from methanol, and recrystallised from benzene–light petroleum in needles, m. p. 127° (decomp.) (Found : C, 80·8; H, 6·1; OEt, 11·4. $C_{25}H_{22}O_3$ requires C, 81·1; H, 6·0; OEt, 12·2%), and had $[\alpha]_D^{20}$ +10·9° (*c*, 2·21 in C_6H_6). It gave a negative test with ferric chloride and a yellow colour with aqueous potassium hydroxide.

The acidic ethereal solution gave on evaporation a mixture of acids (1·4 g.) from which benzoic acid was removed by boiling water. When the water-insoluble residue was digested with *cyclo*hexane, the insoluble portion crystallised from benzene in needles, m. p. 190° (decomp.), identical with *cis*-β-desylcinnamic acid.

When condensation was carried out at room temperature, the yields of the pyrone and the desyl ester were 2·5 g. and 4·6 g., respectively.

Degradation of 4 : 5 : 6-Triphenyl-2-pyrone.—The pyrone (3 g.) was refluxed with 10% methyl-alcoholic potassium hydroxide (40 ml.) for 6 hr., and after removal of the solvent, the residue was diluted with water and extracted with ether. The ethereal solution yielded a residue (0·7 g.) from which 1-oxo-1 : 2 : 3-triphenylbut-2-ene, m. p. 90°, was obtained. The alkaline solution gave on acidification and extraction with ether an acidic mixture (2 g.) from which benzoic acid was removed by boiling water. The residue gave β-benzylcinnamic acid which crystallised from benzene–light petroleum in needles, m. p. 169° (cf. Ruhemann, *loc. cit.*; Spring, *J.*, 1934, 1333). *Methyl* β-*benzylcinnamate*, prepared by diazomethane, crystallised from light petroleum (b. p. 30—50°) in aggregates of needles, m. p. 56° (Found : C, 81·1; H, 6·1; OMe, 12·4. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4; OMe, 12·3%).

Oxidation of the Ketone (IX*c*; R = H).—A solution of 1-oxo-1 : 2 : 3-triphenylbut-2-ene (0·4 g.) in glacial acetic acid (15 ml.) was mixed with a solution of chromic oxide (0·4 g.) in acetic acid (5 ml.) and a few drops of water. The mixture was warmed on the water-bath for 1 hr. and then kept at room temperature overnight. It was poured into water and extracted with ether, and the ethereal solution was shaken with sodium hydrogen carbonate solution which yielded benzoic acid (0·2 g.). The neutral fraction gave on steam-distillation acetophenone which was identified as the 2 : 4-dinitrophenylhydrazone, m. p. 248°.

Ring Fission.—4 : 5 : 6-Triphenyl-2-pyrone (4 g.) was warmed with 5% methyl-alcoholic potassium hydroxide (60 ml.) until it dissolved completely. The orange solution was diluted with water, extracted with ether, and acidified and the sticky precipitate extracted with ether. The acidic product (4 g.), recovered from the ethereal solution, was refluxed with *cyclo*hexane, and the insoluble portion was subjected to fractional crystallisation from benzene, and the fraction, m. p. 180°, which separated first contained cis-β-*desylcinnamic acid*, needles (from benzene), m. p. 190° (decomp.) (Found : C, 80·9; H, 5·3. $C_{23}H_{18}O_3$ requires C, 80·7; H, 5·3%). *Methyl* cis-β-*desylcinnamate*, prepared by diazomethane, crystallised from methanol or benzene–light petroleum in prisms, m. p. 130°, $[\alpha]_D^{20}$ +14·8° (*c*, 2·03 in C_6H_6) (Found : C, 80·7; H, 5·7; OMe, 9·1. $C_{24}H_{20}O_3$ requires C, 80·9; H, 5·7; OMe, 8·7%), giving a negative

test with ferric chloride, a yellowish-orange colour with aqueous potassium hydroxide, and recovered unchanged after being heated with hydroxylamine. *Ethyl* cis-β-*desylcinnamate*, obtained when a suspension of silver *cis*-β-desylcinnamate (1 g.) in benzene was refluxed with ethyl iodide (5 g.) for 2 hr., crystallised from light petroleum in cubes, 93° (Found : C, 81·1; H, 6·0; OEt, 11·4. $C_{25}H_{22}O_3$ requires C, 81·1; H, 6·0; OEt, 12·2%). Both esters were also prepared catalytically and were recovered unchanged after being heated with traces of hydrochloric acid in alcohol. They were readily converted into the pyrone on treatment with 1 mol. of sodium ethoxide in ether, or when their alcoholic solutions were mixed with a few drops of 5% alcoholic potassium hydroxide.

5-Oxo-3 : 4 : 5-triphenylpent-3-enoic acid was obtained from the benzene liquors left after separation of *cis*-β-desylcinnamic acid. It recrystallised from benzene in fine needles, m. p. 149° (decomp.) (Found : C, 80·8; H, 5·5. $C_{23}H_{18}O_3$ requires C, 80·7; H, 5·3%). Its *methyl ester*, prepared by the action of diazomethane and crystallised from benzene–light petroleum, gave two forms of crystals; the few prismatic crystals of methyl *cis*-β-desylcinnamate were mechanically separated from the desired ester, which then crystallised from methanol in rhombs, m. p. 107° (Found : C, 81·1; H, 5·7; OMe, 8·6. $C_{24}H_{20}O_3$ requires C, 80·9; H, 5·7; OMe, 8·7%). Its solution in benzene showed no rotation. This ester was also prepared when ethyl *trans*-β-desylcinnamate (1 g.) in methanol (30 ml.) containing 3 drops of concentrated hydrochloric acid was refluxed for 30 min., during which 0·1 g. of the pyrone separated. The solution was diluted with water and extracted with ether, and the ethereal solution shaken with sodium hydrogen carbonate. The ester recovered from the ethereal solution crystallised from methanol in rhombs, m. p. and mixed m. p. 107° (Found : C, 80·9; H, 5·7; OMe, 8·7%). This ester was quantitatively converted into the pyrone by the action of sodium ethoxide in ether or traces of alcoholic potassium hydroxide.

Ozonolysis of Methyl cis-β-*Desylcinnamate*.—A chloroform solution of the ester (0·5 g.) was treated with ozonised oxygen and, after removal of the solvent, the ozonide was decomposed and distilled with steam. The distillate was extracted with ether, and the extract, which gave a negative ferric chloride test, was shaken with sodium hydrogen carbonate, yielding benzoic acid (0·1 g.). The neutral ethereal solution yielded 0·1 g. of benzil. The non-volatile resinous residue (0·2 g.), which was separated by extraction with ether, contained the unchanged ester, but dibenzoylphenylmethane could not be isolated. When the aqueous solution was neutralised with ammonia, concentrated, and mixed with calcium chloride, the precipitate obtained gave a positive aniline-blue test for oxalic acid (Vogel, " Qualitative Chemical Anaylsis," Longmans, Green and Co., London, 1948, p. 311).

Ozonolysis of Methyl 5-Oxo-3 : 4 : 5-triphenylpent-3-enoate.—The ozonide obtained from this ester (0·5 g.) was decomposed and steam-distilled and the distillate extracted with ether. The ethereal solution was then shaken with sodium hydrogen carbonate, whereby traces of benzoic acid were obtained. The oily residue (0·45 g.) recovered from the ethereal solution yielded benzil (0·25 g.), m. p. and mixed m. p. 95°, on treatment with cold light petroleum. The oil recovered from the light petroleum solution gave a plum colour with ferric chloride and yielded on alkaline hydrolysis and steam-distillation acetophenone which was identified as its 2 : 4-dinitrophenylhydrazone, m. p. 248°.

trans-1-*Oxo*-1 : 2 : 3-*triphenylbut-2-ene* (IX*b*; R = H).—*cis*-β-Desylcinnamic acid (0·5 g.) was heated just above its m. p. and kept at that temperature until carbon dioxide ceased to be evolved. The glassy residue dissolved in boiling light petroleum, leaving traces of the pyrone, and, on cooling, the ketone (0·3 g.) separated. It recrystallised in clusters of prisms, m. p. 105°, depressed on admixture with the isomer (IX*c*; R = H) (Found : C, 88·2; H, 6·3. $C_{22}H_{18}O$ requires C, 88·6; H, 6·1%). This ketone, which was also obtained by heating the acid (VI; R = H) above its m. p., did not react with hydroxylamine.

A chloroform solution of the ketone (0·5 g.) was exposed to ozonised oxygen at −10°, and after evaporation of the solvent the ozonide was decomposed and distilled with steam. The distillate containing a yellow solid and oily droplets was extracted with ether, and the residue (0·45 g.) recovered from the ethereal solution yielded benzil on treatment with cold light petroleum. The petroleum mother-liquor afforded an oil which was converted into a 2 : 4-dinitrophenylhydrazone. It was freed from benzil 2 : 4-dinitrophenylhydrazone by boiling alcohol, and the residue crystallised from acetic acid in red needles, m. p. 248°, identical with acetophenone 2 : 4-dinitrophenylhydrazone. When this ketone was oxidised with chromic oxide as for its isomer (IX*c*; R = H), acetophenone and benzoic acid were obtained.

6-p-*Methoxyphenyl*-4 : 5-*diphenyl*-2-*pyrone*.—4-Methoxydeoxybenzoin (6·5 g.) and ethyl phenylpropiolate (5 g.) were condensed at 0° and the product worked up as before. The pyrone

(3·3 g.) crystallised from benzene in yellowish plates, m. p. 200° (Found: C, 81·5; H, 5·25; OMe, 8·8. $C_{26}H_{14}O_3$ requires C, 81·3; H, 5·1; OMe, 8·8%).

Ethyl trans-β-4-*Methoxydesylcinnamate*.—This ester (4·4 g.) crystallised from benzene–light petroleum in needles, m. p. 151° (decomp.) (Found: C, 78·3; H, 6·0. $C_{26}H_{24}O_4$ requires C, 78·0; H, 6·0%). It gave a negative test with ferric chloride and a yellow colour with aqueous potassium hydroxide. The acidic product of the reaction gave *p*-anisic and *cis*-β-4-methoxydesylcinnamic acids on fractional crystallisation from benzene.

Fission of the Pyrone.—The pyrone (3 g.) was dissolved in warm 5% methyl-alcoholic potassium hydroxide (60 ml.), and most of the alcohol was then distilled. The residue was diluted with water and extracted with ether, and the alkaline solution acidified and extracted with ether. cis-β-4-*Methoxydesylcinnamic acid*, m. p. 170°, recovered from the ethereal solution, crystallised from benzene in needles, m. p. 196° (decomp.) (Found: C, 77·6; H, 5·6. $C_{24}H_{20}O_4$ requires C, 77·4; H, 5·4%). The mother-liquor afforded impure 5-oxo-5-*p*-methoxyphenyl-3 : 4-diphenylpent-3-enoic acid, m. p. 163° (decomp.). *Methyl* cis-β-4-*methoxydesylcinnamate*, prepared by diazomethane, crystallised from methanol in prisms, m. p. 140° (Found: C, 77·0; H, 5·9; OMe, 15·9. $C_{25}H_{22}O_4$ requires C, 77·7; H, 5·7; 2OMe, 16·1%). This ester gave the pyrone on treatment with basic reagents as above.

Methyl 5-p-*Methoxyphenyl*-5-*oxo*-3 : 4-*diphenylpent*-3-*enoate*.—This was prepared when a solution of ethyl *trans*-β-4-methoxydesylcinnamate (0·5 g.) in methanol (20 ml.) containing 2—3 drops of concentrated hydrochloric acid was refluxed for 30 min. After separation of the pyrone (0·15 g.), the *ester* was isolated and crystallised from methanol in needles, m. p. 113° (Found: C, 77·7; H, 5·85; OMe, 16·8. $C_{25}H_{22}O_4$ requires C, 77·7; H, 5·7; 2OMe, 16·1%). This ester was also obtained by fractional crystallisation of the product obtained by methylating the impure pent-3-enoic acid. It gave the pyrone with basic reagents.

trans-1-p-*Methoxyphenyl*-1-*oxo*-2 : 3-*diphenylbut*-2-*ene* (IX*b*; R = OMe).—This *ketone* was isolated from the residue left after decarboxylation of *cis*-β-4-methoxydesylcinnamic acid as before. It crystallised from light petroleum in rhombs, m. p. 100° (Found: C, 83·8; H, 6·4. $C_{23}H_{20}O_2$ requires C, 84·1; H, 6·15%).

5 : 6-*Di*-p-*methoxyphenyl*-4-*phenyl*-2-*pyrone*.—4 : 4′-Dimethoxydeoxybenzoin (7·4 g.) and ethyl phenylpropiolate (5 g.) were condensed at 0° and the product worked up as before. The viscous residue (4·9 g.) recovered from the ethereal solution gave the *pyrone* (3·1 g.) on treatment with methanol. This crystallised from methanol in yellowish cubes, m. p. 153° (Found: C, 78·0; H, 5·3; OMe, 16·2. $C_{25}H_{20}O_4$ requires C, 78·1; H, 5·25; 2OMe, 16·2%).

Ethyl trans-β-4 : 4′-*dimethoxydesylcinnamate* was recovered from the alkaline solution of the product as a reddish-yellow viscous oil (6·8 g.) which solidified on treatment with methanol. It crystallised from benzene–light petroleum in needles, m. p. 150° (decomp.), which gave a yellow colour with potassium hydroxide, and was recovered unchanged from sodium ethoxide (Found: C, 75·5; H, 6·0; OMe, 14·2; OEt, 10·3. $C_{27}H_{26}O_5$ requires C, 75·3; H, 6·1; 2OMe, 14·4; OEt, 10·5%).

Ethyl β-(1-*Benzoyl*-1-*phenylethyl*)*cinnamate*.—*meso*-*C*-Methyldeoxybenzoin (6 g.) and ethyl phenylpropiolate (5 g.) were condensed at 0° in presence of sodium ethoxide (1·95 g.); when the product was worked up, the ethereal solution yielded a viscous oil (9 g.). After being kept in the ice-chest for 3 months, the oil deposited the *ester* (1·2 g.) which crystallised from methanol in cubes, m. p. 113° (Found: C, 81·4; H, 6·15. $C_{26}H_{24}O_3$ requires C, 81·2; H, 6·3%).

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A Study by the Gouy Interference Method of the Diffusion in Water of Potassium Laurate.

By N. Brudney and L. Saunders.

[Reprint Order No. 6140.]

The rate of diffusion of potassium laurate in salt-free aqueous solutions at various concentrations has been measured by means of the Gouy interference method. The mean diffusion coefficient falls rapidly with increasing concentration above the critical concentration for micelle formation, to a minimum value. The diffusion coefficient then rises again to an almost constant value in concentrated solutions. Anomalous interference patterns were obtained above the critical concentration.

A method for determining weight-average diffusion coefficients for heterogeneous solutions has been applied to the anomalous patterns. Theoretical diffusion coefficients have been calculated, based on a simple mass-law interpretation and fair agreement with the experimental results has been found. The obscuration of the minimum in the diffusion coefficient–concentration curve by the addition of electrolytes is discussed.

Diffusion measurements were used in the investigation of the structure of aqueous solutions (or sols) of potassium laurate by McBain and Liu (*J. Amer. Chem. Soc.*, 1931, **53**, 59). Laing-McBain (*ibid.*, 1933, **55**, 545) used sodium oleate as the association colloid and concluded that the primary particles of this paraffin-chain salt were not much larger than those of potassium laurate. The earliest intensive diffusion measurements with the anionic soaps were made by Jander and Weitendorf (*Angew. Chem.*, 1934, **47**, 197) who, using sodium laurate and sodium decanoate, postulated the formation of bimolecular aggregates before the formation of micelles in these solutions. Hartley and Runnicles (*Proc. Roy. Soc.*, 1938, *A*, **168**, 420) measured the diffusion of cetylpyridinium chloride in the presence of a swamping excess of simple electrolyte with a sintered-disc cell, but found that the diffusion of anionic soaps in this type of apparatus led to erroneous results owing to the build-up of a structure in the glass disc. They suggested the use of a free-boundary method in the determination of diffusion constants for the normal paraffin-chain soaps. Such a method was applied to lauric acid salts in the absence of added electrolyte (Lamm and Högberg, *Kolloid Z.*, 1940, **91**, 10) and in a salt-containing medium (Lamm, *ibid.*, 1942, **98**, 45; Granath, *Acta Chem. Scand.*, 1950, **4**, 103). The diffusion of potassium laurate by tagging it with dyes has been studied by Hoyer and Mysels (*J. Phys. Colloid Chem.*, 1950, **54**, 966) in the presence of excess of alkali.

In the present work, Gouy's interference method (Longsworth, *J. Amer. Chem. Soc.*, 1947, **69**, 2510; Saunders, *J.*, 1953, 519) has been used to examine the diffusion of potassium laurate in a salt-free medium.

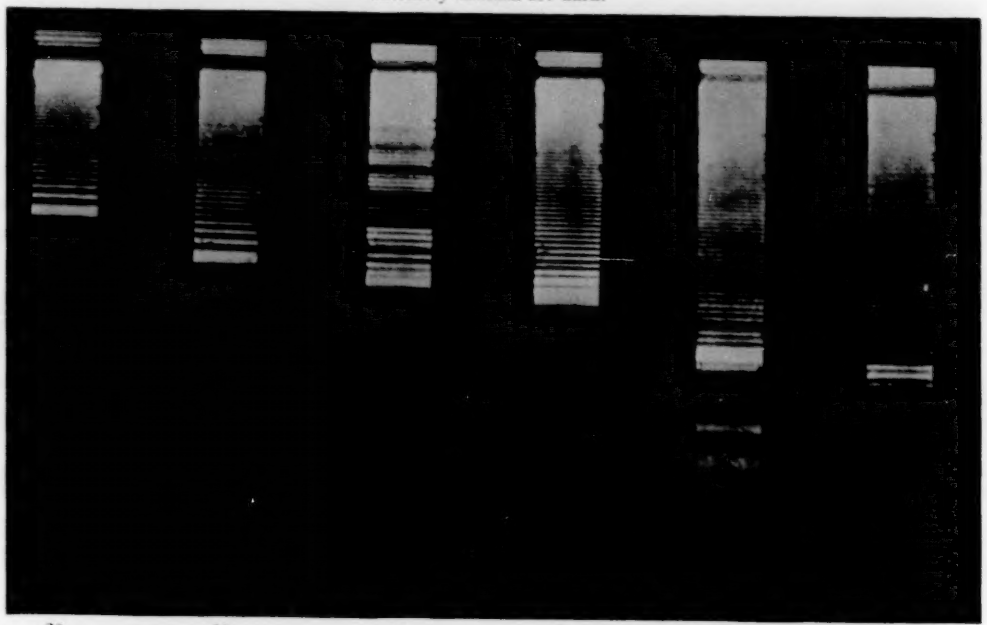
Experimental

Materials.—Lauric acid (Eastman Kodak) had equiv. 200·5, determined potentiometrically, and m. p. 42—43°. The acid was neutralised with a solution of " AnalaR " potassium hydroxide from which traces of carbonate were removed by ion-exchange. Sols were allowed to " age " for at least 24 hr. before use. Little trouble was experienced with hydrolysis, except in solutions containing less than 20 mmoles/l. : to these solutions a small excess of alkali was added.

Diffusion Coefficients.—The sol–water boundary was formed in a metal cell which has replaced the all-glass cell used in the apparatus previously described (Saunders, *loc. cit.*). This metal cell, made in these laboratories, of nickel-coated brass, is fitted with two windows made of half-wavelength optical flats. The 50-micron slit through which the two liquids are drawn is made of two nickel-coated brass blocks spaced with platinum foil. The whole of the interior of the cell is Silicone-coated by the hydrolysis of methylchlorosilane. The two liquids are introduced into the cell by means of motor-driven syringes, whose glass needles reach to the top of the cell windows. This method has replaced the pipettes and rubber tubing used in the

Gouy patterns for the diffusion of potassium laurate into water taken 1800 *seconds after diffusion has started.*

Intensity minima are dark.



Concentration 20 25 28 30 40 45

[*To face p.* 2917.

earlier apparatus and permits easier control of the rate of the inflowing liquids. For more rapidly diffusing materials a very fast photographic plate (Kodak P 2000) has been used to record the Gouy patterns, permitting a reduction of exposure time. Apart from these alterations, the apparatus and calculation of diffusion coefficients are as previously described. Values of average diffusion coefficients for potassium laurate solutions are shown in Table 1 (concentrations in mmoles/l.; diffusion coefficients in cm.²/sec. at 25°).

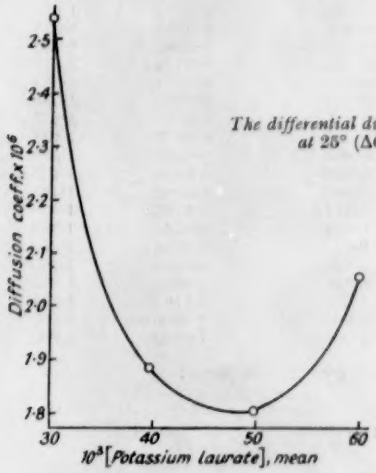
Table 1. *Diffusion of potassium laurate into water.*

(For meaning of symbols, see *J.*, 1953, 519.)

Concn.	20·0	22·5	25·0	28·0	30·0	35·0	40·0	45·0
j_m	34·5	38·5	42·6	51·9	54·9	61·6	68·1	73·8
10^6D	8·31	8·31	8·24	8·26	7·92 *	6·75 *	5·81 *	5·13 *

* C_t constant over a limited range between the optic axis and the anomalous intensity region, see Plate.

Above the critical concentration for micelle formation (CMC) of 28 mmoles/l., the diffusion coefficient decreased rapidly with increasing concentration. The patterns obtained with solutions below the CMC were quite normal in appearance (see Plate). At the CMC, the pattern appeared diffuse and the intensities of the lines varied throughout the pattern, but with some



The differential diffusion of potassium laurate at 25° (ΔC = 10 mmoles/l.).

regularity in the variation. Above the CMC, the pattern was again normal but for two or three very intense maxima, indicating heterogeneity in the diffusing solution. Lamm and Högberg (*loc. cit.*) observed that the calculation of diffusion coefficients when using these solutions above the CMC was very uncertain owing to heterogeneity.

To overcome this difficulty, differential diffusion measurements were made (see Table 2 and Figure).

TABLE 2. *Differential diffusion of potassium laurate.*

Concn. of lower sol	Concn. of upper sol or solution	j_m	10^6D_A	$10^6D'$	Concn. of lower sol	Concn. of upper sol or solution	j_m	10^6D_A	$10^6D'$
35·0	25·0	15·39	—	2·545	65·0	55·0	14·93	—	2·06
40·0	0·0	68·17	4·55	5·71	70·0	50·0	31·59	—	2·35
50·0	30·0	31·15	—	2·055	80·0	60·0	31·63	—	2·63
50·0	0·0	85·00	2·90	4·66	80·0	40·0	62·45	—	2·45
50·0	10·0	65·38	2·42	4·11	100·0	60·0	62·33	—	2·85
52·5	47·5	7·18	—	1·61	150·0	110·0	61·80	—	3·71
53·75	46·25	11·23	—	1·72	200·0	160·0	61·24	—	4·34
55·0	45·0	14·76	—	1·80	300·0	260·0	60·27	—	4·55
60·0	40·0	31·09	—	2·13	400·0	360·0	60·18	—	4·65
60·0	20·0	64·45	1·92	2·53					

D_A = Height-area average diffusion coefficient. D' = Weight-average diffusion coefficient.

Patterns obtained from differential diffusion measurements showed no intensity anomalies, except when the concentration of the upper solution was less than the CMC.

A method for determining diffusion coefficients of heterogeneous solutions by the use of a relative fringe deviation graph (Akeley and Gosting, *J. Amer. Chem. Soc.*, **1953**, **75**, 5685) has been applied to these patterns. These authors' symbols being used, the results of an examination of the relative fringe deviation graph for the diffusion of a sol, of 40 mmoles/l., of potassium laurate into water are shown in Table 3.

TABLE 3. *Examination of the relative fringe deviation graph for the diffusion of* 40 *mmoles/l. of potassium laurate into water.*

$f(\zeta)$	$d\Omega/df(\zeta)$	Ω	$1-\Omega/e^{-\zeta^2}$	$\left[1+\frac{2}{\sqrt{\pi}}\zeta\left(\frac{d\Omega}{df(\zeta)}\right)\right]^4$	H	$H\left[\frac{2}{\sqrt{\pi}}\zeta\right]^4 e^{-\zeta^2}$
0·01	9·6	0·041	0·957	167·19	0·0057	0·0000285
0·025	0·702	0·064	0·929	2·522	0·368	0·0062
0·05	0·452	0·082	0·902	2·1715	0·415	0·0175
0·075	0·279	0·090	0·886	1·7679	0·501	0·0357
0·10	0·000	0·094	0·874	1·0000	0·874	0·0903
0·15	−0·170	0·086	0·872	0·5968	1·461	0·2529
0·20	−0·176	0·076	0·874	0·5449	1·604	0·3973
0·25	−0·161	0·068	0·875	0·5432	1·611	0·5236
0·30	−0·154	0·060	0·878	0·5304	1·655	0·6671
0·35	−0·145	0·053	0·880	0·5265	1·671	0·8031
0·40	−0·131	0·046	0·883	0·5397	1·636	0·9098
0·45	−0·120	0·039	0·888	0·5493	1·617	1·016
0·50	−0·107	0·034	0·889	0·5695	1·561	1·085
0·55	−0·094	0·028	0·895	0·5935	1·508	1·139
0·60	−0·084	0·025	0·891	0·6134	1·453	1·172
0·65	−0·081	0·021	0·892	0·6076	1·468	1·242
0·70	−0·079	0·017	0·894	0·6000	1·490	1·298
0·75	−0·072	0·013	0·899	0·6096	1·475	1·294
0·80	−0·068	0·009	0·908	0·6082	1·493	1·280
0·85	−0·060	0·006	0·914	0·6263	1·459	1·171
0·90	−0·048	0·004	0·909	0·6685	1·360	0·946
0·925	−0·044	0·0025	0·921	0·6788	1·357	0·831
0·95	−0·037	0·0015	0·928	0·7086	1·305	0·649
0·975	−0·027	0·0005	0·946	0·7613	1·243	0·411
0·99	−0·019	0·0000	1·000	0·8107	1·234	0·211
0·995	approaching zero	zero	1·000	1·0000	1·000	0·1089
0·999	approaching zero	zero	1·000	1·0000	1·000	0·1315

The following integrals were evaluated by suitable plots:

$$\int_0^1 (H-1)\,df(\zeta) = 0.39$$

$$\int_{\zeta=\infty}^{0} \left(\frac{2}{\sqrt{\pi}}\zeta\right)^4 H e^{-\zeta^2} d\left[\frac{d\Omega}{df(\zeta)}\right] = -0.086$$

Akeley and Gosting (*loc. cit.*) have shown, taking $s = 1$, that

$$\bar{D}' = D_A'\left\{1 + \int_0^1 (H-1)\,df(\zeta) + \frac{\pi}{2}\int_{\infty}^{0}\left[\frac{2}{\sqrt{\pi}}\zeta\right]^4 e^{-\zeta^2} H\, d\left[\frac{d\Omega}{df(\zeta)}\right]\right\}$$

$$\bar{D}' = 4.552 \times 10^{-6}\,[1 + 0.39 + 1.571(-0.086)]$$

$$= 5.71 \times 10^{-6}$$

The close agreement between this value and the approximate value given in Table 1 is noteworthy. The integrals used in the calculation above, and others like it, were large compared with those of Akeley and Gosting and the possibility of error in their graphical evaluation was therefore increased. The values of Ω were quite large (almost 0·1) and Ω tended to increase with increasing concentration difference between lower and upper solution (Δc). Large values of Ω were thought to be the reason for the failure of an attempt to apply Ogston's method for examination of heterogeneous diffusion patterns (*Proc. Roy. Soc.*, **1949**, *A*, **196**, 272) which did not seem to permit evaluations of large deviations from Gaussian form.

From these results and those shown in Table 2 a number of observations can be made. The diffusion coefficient varies with concentration and also with Δc (see Table 4). A plot of

TABLE 4. *The variation of diffusion coefficient with* Δc.

Mean concn. of upper and lower soln....	40	40	50	50	50	50	60	60
Δc	40·0	20·0	20·0	10·0	7·5	5·0	40·0	20·0
$10^6D'$	2·53	2·055	2·13	1·80	1·72	1·61	2·45	2·35

Δc against diffusion coefficient at a mean concentration of 50 mmoles/l. (the minimum on the diffusion coefficient–concentration curve, see Fig.), on extrapolation to $\Delta c = 0$, gave $D' = 1{\cdot}43 \times 10^{-6}$. This value has been considered to be the true diffusion coefficient of the micellar form since, as Δc approaches zero, electrical effects are minimised.

Theoretical diffusion coefficients for potassium laurate solutions of concentrations up to 50 mmoles/l. have been calculated, based on the following assumptions :

(i) That the law of mass action without activity coefficients can be applied to the equilibrium between simple laurate ions and micelles; this leads to the equation

$$\log C_2 - n \log C_1 = \text{constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where C_2 and C_1 are the concentrations of micelles and simple laurate respectively in any solution and n is the mean aggregation number of the micelle.

(ii) That the value $D_2 = 1{\cdot}43 \times 10^{-6}$ represents the true diffusion coefficient of the micellar form; this gave n a value of **52·3**, by application of the Stokes–Einstein equation.

(iii) In a solution of concentration 25 mmoles/l., all the laurate is present in the simple form.

The value of the constant in equation (1) was determined by using the experimental diffusion coefficient for 35 mmoles/l. diffusing into a 25 mmoles/l. solution ($D' = 2{\cdot}545 \times 10^{-6}$). If D_1 is the diffusion coefficient of simple laurate, determined in measurements on dilute solutions, then

$$D' = \alpha D_2 + (1-\alpha)D_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where α is the refractive index fraction of micellar form in the diffusing laurate (*i.e.*, in the laurate between 35 and 25 mmoles/l.). From a knowledge of the refractive index increment per unit concentration of simple and micellar forms, which can be derived from the experimental values of j_m, α was converted into a concentration fraction x; then, by assumption (iii), C_1 and C_2 for the 35 mmoles/l. solution were calculated. From these and similar calculations based on the diffusion of 45 into 35 mmoles/l., and 55 into 45 mmoles/l., and the value of n, the constant for equation (1) was derived. Equation (1) was then used to calculate values of C_2 corresponding to given values of C_1, from which a table of $C_1 + C_2$ and x values was drawn up [$x = C_2/(C_1 + C_2)$]. This Table showed that assumption (iii) was not quite correct, and that a solution of concentration 25 mmoles/l. had a small value of x. Successive approximations were therefore used to give a final value to the constant for equation (1), *viz.*,

$$\log C_2 = 52{\cdot}3 \log C_1 = -73{\cdot}455.$$

Values of C_1, C_2, $(C_1 + C_2)$, and x obtained by using this equation are shown in Table 5; x begins to increase rapidly for total laurate concentrations between 26·5 and 29·5 mmoles/l., which is in agreement with the CMC derived from the diffusion measurements.

TABLE 5. *Relationship of* C_1 *and* C_2 *based on the equation* $\log C_2 - 52{\cdot}3 \log C_1 = -73{\cdot}455$.

C_1	C_2	$C_1 + C_2$	x	C_1	C_2	$C_1 + C_2$	x	C_1	C_2	$C_1 + C_2$	x
24·6	0·19	24·79	0·008	26·0	3·55	29·55	0·121	26·8	17·18	43·98	0·391
24·8	0·30	25·10	0·012	26·2	4·59	30·79	0·149	27·0	25·53	52·53	0·486
25·0	0·45	25·45	0·018	26·4	7·85	34·25	0·229	27·2	37·58	64·78	0·580
25·5	1·01	26·51	0·038	26·6	11·67	38·27	0·305	27·4	55·21	82·61	0·668

By means of this Table, the theoretical diffusion coefficients for the experiments carried out with solutions of less than 50 mmoles/l. were calculated, by the reverse process to that

TABLE 6. *Comparison of experimental and theoretical diffusion coefficients.*

Solution concns.	Diffusion coeff. $\times 10^6$ theoretical	exptl.	Solution concns.	Diffusion coeff. $\times 10^6$ theoretical	exptl.	Solution concns.	Diffusion coeff. $\times 10^6$ theoretical	exptl.
52·5/47·5	1·6	1·6	55/45	1·6	1·8	50/30	1·8	2·05
53·75/46·25	1·6	1·7	45/35	1·7	1·9	40/0	6·2	5·7
50/10	4·6	4·1	35/25	2·7	2·55	50/0	5·4	4·7

outlined above for determining the constant of equation (1). In Table 6 these theoretical results are compared with the observed values.

Discussion

The results show that the diffusion coefficient–concentration curve for potassium laurate, which is constant in dilute solution, falls off rapidly after the CMC at 28 mmoles/l., to a minimum value at 50 mmoles/l., and then rises again to a constant value at concentrations greater than 200 mmoles/l. (see Tables 1 and 2 and Fig.). This second constant value is approximately half the value of the diffusion coefficient in dilute solution. A similar minimum has been observed in the diffusion coefficient–concentration curves for some sulphonic acids (Laing-McBain, *Proc. Roy. Soc.*, 1939, *A*, **170**, 415). Lamm and Högberg (*loc. cit.*) did not find a minimum in the diffusion coefficient–concentration curve for sodium laurate, but they only used solutions of mean concentrations not greater than 75 mmoles/l. of sodium laurate. The limited solubility of sodium laurate at 20° prevented these authors from using greater concentrations and so only two measurements at mean concentrations greater than 50 mmoles/l. were made. Using the more soluble potassium laurate and a higher temperature, we were able to show this minimum. Other diffusion measurements on anionic soaps, by Lamm, Granath, and McBain (*locc. cit.*), have all been carried out in the presence of a swamping excess of simple electrolyte and excess of alkali, which seems to have obscured the minimum.

The effect of adding electrolytes to soap solutions has been discussed by many authors. Some state that added electrolyte has no effect on the size and aggregation number of association colloids (*e.g.*, Hutchinson, *J. Colloid Sci.*, 1954, **9**, 191; Stainsby and Alexander, *Trans. Faraday Soc.*, 1950, **46**, 587); others (*e.g.*, Debye, *J. Phys. Colloid Chem.*, 1949, **53**, 1, and Yurzhenko and Kucher, *Kolloid. Zhur.*, 1952, **14**, 219) have found that micellar weight increases considerably with the addition of simple electrolyte, indicating either an increase in size, or aggregation number of micelles, or both. Further, addition of different electrolytes of equal ionic strength seems to alter the properties and structure of the sol (Granath, *loc. cit.*). In view of this and the differences of opinion on the effect of salt addition, some doubt must be cast on the value of estimates of micellar size and aggregation number derived from measurements of physical properties in salt-containing media. A further difficulty is the large amount of alkali that must be added to salt-containing soap solutions to keep the soap in solution. Lamm and Högberg (*loc. cit.*) have pointed out the disadvantage of the considerable increase in ionic strength required to maintain solution and the effect that these alien ions have on the micelles.

The results of the present measurements are interpreted as follows. Below the critical concentration, the laurate is present almost entirely in the simple ion form. Between the critical concentration and the concentration at the minimum on the diffusion coefficient–concentration curve, a concentration limit (Ekwall, *J. Colloid Sci.*, 1954, Suppl. 1, 66), there is a considerable increase in the concentration of laurate in micelles (C_2), but little increase in the concentration of simple ions (C_1) (see Table 5). The steady decrease of diffusion coefficient with this increasing concentration of micelles indicates that the micelles are of uniform size, and the data seem consistent with the idea that the micelle is the spherical particle described by Hartley (*Quart. Rev.*, 1948, **2**, 152; *Nature*, 1949, **163**, 767). The results obtained when the concentration limit is exceeded are consistent either with the idea of a break up of the spherical particles to form smaller platelets or discs as has been described by Booij ("Colloid Science," Kruyt, Elsevier Publ. Co. Inc., New York, Vol. II, p. 701) or with Hartley's conception of the single spherical particle, the diffusion coefficient of which varies with concentration, not because of the particle itself, but because of the changing effect of the gegenions upon the micelle (*Trans. Faraday Soc.*, 1939, **35**, 1109).

The general agreement of order between theoretical and experimental values of diffusion coefficients for solutions below the concentration limit seems to confirm that the simple mass-law interpretation in this region is justified as a rough approximation. The larger discrepancy between theoretical and experimental values for diffusion coefficients calculated by means of Akeley and Gosting's method (*loc. cit.*) can be attributed both to the large

errors that occur in graphical integration of results showing a large value for the relative fringe deviation (Ω) and to the electrical effects when Δc is large.

The aggregation number used here for the calculation of theoretical diffusion coefficients is 52·3. The theoretical diffusion coefficients were very sensitive to small changes in this aggregation number; a variation of one or two units increased the discrepancies between experimental and theoretical values. This appears to confirm that the correct aggregation number has been used. Other estimates of the aggregation number recorded in the literature vary from 63 ± 8 (Anderson and Carpenter, *J. Amer. Chem. Soc.*, **1953**, **75**, 850) to 170 (Hoyer and Mysels, *loc. cit.*), although in both of these cases measurements were made at concentrations much greater than the concentration limit at 50 mmoles/l.

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Kinetics and Mechanism of Aromatic Halogenation by Hypohalous Acids. Part II. Directive Effects of Substituents in the Bromination of Aromatic Ethers by Hypobromous Acid.*

By S. J. BRANCH and BRYNMOR JONES.

[Reprint Order No. 6159.]

A kinetic study of the bromination of a wide range of aromatic ethers by hypobromous acid in 75% acetic acid has shown that the relative directive influences of *m*-alkoxy-groups are in close agreement with the values found earlier in the chlorination of similar ethers in 99% acetic acid.

The effects of substituents both in the alkyl group and in the phenyl nucleus on the rate of bromination have been studied. With halogen substituents the rates decrease in the order F > Br > Cl, a result which provides additional evidence for a mesomeric electron release in the halogens which is greater in fluorine than in bromine and chlorine. Experiments on iodo-ethers were complicated by the intrusion of a secondary reaction between the iodine atom and the hypobromous acid.

ONCE it had been established that the bromination of aromatic ethers, such as *p*-nitroanisole and *p*-nitrophenetole, by hypobromous acid in 75% acetic acid is a reaction of the first order with respect to each of the reactants (cf. Part I *), and well suited to accurate measurement, it became possible to extend the kinetic study to a wide variety of mono-, di-, and poly-substituted aromatic ethers, and to analyse the rate constants obtained in terms of the parameters of the modified Arrhenius equation, $k = PZ \exp(-E/RT)$. This makes it possible to enlarge existing knowledge of the rates of nuclear substitution and also affords an opportunity to compare the reactivity of a carefully selected family of compounds with different electrophilic reagents—in this case the chlorine molecule and the brominium ion Br^+, or its solvated form, H_2OBr^+. Earlier attempts to study bromination in 50% acetic acid with bromine were complicated by the formation of HBr_3, the reaction undergoing a marked retardation as hydrogen bromide was liberated or when it was added initially (cf. *J.*, 1929, 2810).

The rate constants now obtained for the bromination of a variety of phenyl ethers by hypobromous acid in 75% acetic acid solution at 20°, are summarised in Tables 1 and 2. In all cases the reaction was of the second order, and satisfactory constants were obtained over 80—90% of the reaction range.

* Part I, *J.*, 1954, 2317.

TABLE 1. *Rate constants for the reaction of the ethers* 1 : 2 : 4-$RO{\cdot}C_6H_3XY$ *with hypobromous acid in* 75% *acetic acid.* Values of $k_{20°}$ (l. $mole^{-1}$ $sec.^{-1}$).

X	Y	R: Me	Et	Pr^n	Bu^n	Am^n	Pr^i	Bu^i	Am^i	CH_2Ph
H	NO_2	0·162	0·330	0·353	0·360	0·359	0·642	—	—	0·113
Cl	Cl	0·283	0·566	0·634	0·645	0·652	1·034	—	—	0·205
Br	Br	0·373	0·747	0·852	0·860	0·880	1·36	1·01	0·974	0·265
Cl	CO_2Et	0·0648	0·130	0·145	0·153	0·153	0·224	—	—	—
Br	CO_2Et	0·0881	0·177	0·200	0·205	0·206	0·319	—	—	—
Cl	CO_2Me	0·0626	0·124	0·140	—	—	0·208	—	—	—
Br	CO_2Me	0·0840	0·166	0·192	—	—	0·305	—	—	—
CO_2Me	Cl	0·256	—	—	—	—	0·840	—	—	—
CO_2Me	Br	0·345	0·686	—	—	—	1·02	—	—	—

X	Y	R: $[CH_2]_2Br$	$[CH_2]_3Br$	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	*o*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	$CH_2{\cdot}CO_2H$ *	$[CH_2]_2CO_2H$	$CHMe{\cdot}CO_2H$
Cl	Cl	0·0455	0·160	—	—	0·0230	0·136	0·0274
H	F	—	—	—	15·6	9·5	—	—
H	Cl	—	—	11·7	9·5	4·1	35	5·0
H	Br	—	—	—	—	5·6	51	—

* Methyl ester = 0·102.

TABLE 2. *Rate constants for the reaction of di- and poly-substituted phenyl ethers (conditions as in Table* 1).

Series	R: Me	Et	CH_2Ph	$CH_2{\cdot}CO_2H$	$CHMe{\cdot}CO_2H$
2 : 6-Dichlorophenyl	—	—	—	—	0·003
2 : 6-Dibromophenyl	0·008	—	—	—	—
2 : 4-Dichloro-3 : 5-xylyl	—	—	—	3·1	—
4-Chloro-2-nitro-3 : 5-xylyl	0·742	1·42	0·493	—	—

The values of the relative directive powers derived from these rate constants are given in Tables 3 and 4. The effects of variations in the alkyl of the alkoxy-group upon the rates of bromination of the ethers $RO{\cdot}C_6H_3XY$ are expressed in the form $100k_{XY}^{OR}/k_{XY}^{OMe}$, where k_{XY}^{OR} and k_{XY}^{OMe} are the rates of substitution of 1 : 2 : 4-$RO{\cdot}C_6H_3XY$ and of the corresponding methyl ether, respectively.

TABLE 3. *Relative directive influences of alkyl groups in the bromination of ethers* 1 : 2 : 4-$RO{\cdot}C_6H_3XY$ *by hypobromons acid in* 75% *acetic acid.* Values of $100k_{XY}^{OR}/k_{XY}^{OMe}$.

X	Y	R: Et	Pr^n	Pr^i	Bu^n	Bu^i	Am^n	Am^i	Octyl^n
H	NO_2	204	219	396	223	—	223	—	218
Cl	Cl	201	224	365	228	—	231	—	—
Br	Br	200	229	366	231	271	236	262	—
Cl	CO_2Et	201	224	345	236	—	236	—	—
Br	CO_2Et	201	227	362	233	—	234	—	—
Cl	CO_2Me	198	224	331	—	—	—	—	—
Br	CO_2Me	198	229	362	—	—	—	—	—
CO_2Me	Cl	—	—	328	—	—	—	—	—
CO_2Me	Br	199	—	296	—	—	—	—	—
	Mean	200	225	—	230	271	232	262	218
Mean values in chlorination *		199	223	440	223	216	221	—	207

* Brynmor Jones, *J.*, 1935, 1832.

Discussion.—The influences of alkoxy-groups on the rates of reaction are in the order *n*-PrO > EtO > MeO. This sequence was to be expected from the studies on chlorination, but the data in Table 3 show a striking similarity between the values in the two reactions (Brynmor Jones, *J.*, 1935, 1831). Although bromination and chlorination are analogous processes, it could not be foreseen that the relative directive effects of so wide a range of alkoxy-groups would be so similar, especially since in bromination in 75% acetic acid the attacking reagent is either the brominium ion or the solvated cation H_2OBr^+ (Branch and Brynmor Jones, *J.*, 1954, 2317), while in chlorination it is the chlorine molecule. By contrast, bromination of the ethers *p*-$RO{\cdot}C_6H_4X$ in 50% acetic acid containing an excess of hydrogen bromide gave values of MeO : EtO : PrᵢO of 100 : 231 : 711 (cf. *J.*, 1929, 2810),

while in the nitration of the ethers *p*-RO·C_6H_4·OMe the values were 100 : 164 : 180 (Robinson and Smith, *J.*, 1926, 392).

As in chlorination, there is a point when further increase in the chain length of the group R is accompanied by a slight fall in the directive effect of the alkoxy-group. This is shown here at the octyl ether, but in chlorination the decrease becomes more marked as the chain is lengthened to cetyl (Brynmor Jones, *loc. cit.*). In the nitration of quinol ethers, on the other hand, the cetyl ether has the highest reactivity of all the *n*-alkyl ethers.

The effect of branching in the alkyl chain is, in general, very similar in both halogenation reactions. Progressive substitution of the methyl group results in substantial increases in the rates of reaction. The *iso*propoxy-group, however, is unique among alkoxy-groups in that its directive influence not only varies in the same reaction from one series of ethers to another, but also in that the values differ appreciably from one reaction to another (cf. *J.*, 1938, 1854; 1954, 1775).

All attempts to prepare a *tert.*-butyl ether in the state of purity demanded by this kind of investigation failed because of decomposition during distillation, and no firm value of the rate constants could be obtained.

The influence of an electron-attracting bromine atom and of a carboxyl group in modifying the directive power of an alkoxy-group is shown in Table 4. These values reveal a difference in relative directive powers of the O·$[CH_2]_n$·Z groups in passing from the simple *p*-substituted ethers to the 2 : 4-disubstituted compounds. This was not observed in chlorination when the alkoxy-groups were the simple ones.

TABLE 4. *Effect of electron-attracting substituents in the alkyl group.* Values of $100k_{XY}^{OR}/k_{XY}^{OMe}$ for the compounds ArO·$[CH_2]_n$·Z.

Z	Ether	$n = 1$	$n = 2$	Z	Ether	$n = 1$	$n = 2$
CO_2H	*p*-Chlorophenyl	6	52	CO_2H	2 : 4-Dichlorophenyl	8	48
,,	*p*-Bromophenyl	6	55	CH_2Br	2 : 4-Dichlorophenyl	16	59

The results in this table illustrate too the familiar "damping effect" of saturated hydrocarbon chains on the transmission of the influence of a polar substituent (Ingold, *Ann. Rep.*, 1926, **23**, 134). This effect can be measured by the percentage change in directive power which occurs in passing from, for instance, ArO·$[CH_2]_n$·Et to ArO·$[CH_2]_n$·Pr^i.

TABLE 5. *The damping effect of hydrocarbon chains on the transmission of an inductive effect; relative directive powers in the ethers* 1 : 2 : 4-RO·C_6H_3XY. Values of $100k_{XY}^{OR}/k_{XY}^{OMe}$.

R :	Me	Et	Pr^i	Pr^n	Bu^i	Bu^n	Am^i
	100	200	366	225	271	228	236
Increase, %, in directive power		83		20		3·5	

The values for this increase are similar to those for the percentage of *m*-isomer formed in the nitration of Ar·$[CH_2]_n$·$\overset{+}{N}Me_3$ (Ingold, *Rec. Trav. chim.*, 1929, **48**, 805).

The benzyl ethers studied have directive powers close to the mean value found in chlorination (Table 6); the types contained a single powerful deactivating nitro-group, two halogen atoms, or a nitro-group and a halogen atom. The directive influences of the substituted benzyloxy-group in the few *p*-halogenophenyl ethers examined (Table 7) were also in fair agreement with previous values, although the rate of bromination of these ethers is extremely rapid, and the results have not therefore the same accuracy as those for ethers having lower rates of substitution.

Effect of Nuclear Substituents.—The very high reactivities of monosubstituted ethers with hypobromous acid in 75% acetic acid make it impossible to measure directly the relative effects of most *p*-substituents, but the required values may be obtained from the measured rates for certain 2 : 4-disubstituted ethers if the simple additive relation, $k_X^{OR}/k_{XY}^{OR} = k_X^{OMe}/k_{XY}^{OMe}$, is assumed to exist between the effects of substituent groups.

For example, the rates of bromination of *p*-chlorophenoxy- and 2 : 4-dichlorophenoxy-acetic acids are 4·1 and 0·023 l. mole^{-1} sec.$^{-1}$, respectively, and, since that of 2 : 4-dichloroanisole is 0·283, the calculated value for *p*-chloroanisole is 50·4 l. mole^{-1} sec.$^{-1}$. From the

values thus calculated (Table 8) it is seen that the relative rates are in the same order as that for chlorination, namely, $NO_2 < CO_2Me < CO_2Et < Cl < Br < F(<H)$.

The order calculated for the halogens, $Cl < Br < F$, has been confirmed by direct measurements (Table 9), and it affords additional evidence for a mesomeric electron release increasing from bromine to fluorine.

TABLE 6. *Relative directive influence of the benzyl group in the ethers* $ArO{\cdot}CH_2Ph$. Values of $100k^{O\cdot CH_2Ph}/k^{OMe}$.

Ar	Bromination by HOBr	Chlorination
p-Nitrophenyl	70	—
2 : 4-Dichlorophenyl	72	68 *
2 : 4-Dibromophenyl	71	64 *
4-Chloro-2-nitro-3 : 5-xylyl	67	—

* Cf. *J.*, 1931, 2903.

TABLE 7. *Relative directive powers of groups in the ethers* (I) p-$RO{\cdot}C_6H_4X$ *and* (II) 1 : 2 : 4-$RO{\cdot}C_6H_3X_2$.

R :	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	*o*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	$CH_2{\cdot}CO_2H$	$[CH_2]_2{\cdot}CO_2H$	$CHMe{\cdot}CO_2H$
(I; X = F)	—	15	9	—	—
(I; X = Cl)	21	17	8	61	19
(I; X = Br)	—	—	8	64	—
(II; X = Cl)	—	—	8	48	9

TABLE 8. *Calculated velocity constants for bromination of the ethers* p-$MeO{\cdot}C_6H_4X$.

X :	F	Cl	Br	CO_2Me	CO_2Et	NO_2
k_{25} (l. mole^{-1} sec.$^{-1}$)	108	50·4	68	11·1	11·5	0·16

TABLE 9. *Relative directive influences of the halogens.* Values of $100\ k_X^{OR}/k_{Cl}^{OR}$.

Series	Substituent Br	Substituent F	Series	Substituent Br	Substituent F
2 : 4-Disubstituted-phenyl alkyl ethers	135	—	2-Chloro-4-halogenoanisoles	130	—
p-Halogenophenoxyacetic acids	137	232	2-Bromo-4-halogenoanisoles	132	223
p-Halogenophenyl *o*-nitrobenzyl ethers	—	170 (approx.)	*p*-Halogenoanisoles (calc.) ...	135	217

EXPERIMENTAL

The acetic acid and hypobromous acid used in the kinetic experiments were purified by the methods given in Part I.

Most of the alkyl phenyl ethers were prepared by the following method. To the phenol (1·0 mole) in *cyclo*hexanone, anhydrous potassium carbonate (5—8 moles) and the alkyl iodide (1·2 moles) were added, and the solution was refluxed until a heavy sediment settled (usually 1—3 hr.). The sediment was filtered off and washed with acetone, and, after removal of the solvents from the filtrate, the residue was diluted with water and extracted with ether. The ether extract was washed successively with sodium hydroxide solution, water, sulphuric acid, and water, and dried (Na_2SO_4). The ether was then removed and the aromatic ether fractionated under reduced pressure. The physical constants of the ethers (and analyses in the case of new compounds) are recorded in Table 10.

2-Bromoethyl 2 : 4-dichlorophenyl ether, b. p. 134°/2 mm., was prepared in 50% yield by refluxing 2 : 4-dichlorophenyl and excess of potassium carbonate with ethylene dibromide in acetone (Found: C, 35·65; H, 2·6. $C_8H_7OCl_2Br$ requires C, 35·6; H, 2·6%). Appreciable quantities of 1 : 2-bis-(2 : 4-dichlorophenoxy)ethane, m. p. 134°, were also obtained.

3-Bromopropyl 2 : 4-dichlorophenyl ether, b. p. 148°/2 mm., was prepared similarly (Found: C, 38·0; H, 3·6. $C_9H_9OCl_2Br$ requires C, 38·1; H, 3·5%). Here only a trace of 1 : 3-bis-(2 : 4-dichlorophenoxy)propane, m. p. 94°, was isolated.

β-2 : 4-Dichlorophenoxypropionic acid, prepared by refluxing β-chloropropionic acid with 2 : 4-dichlorophenol in aqueous potassium hydroxide, had m. p. 93° after two crystallisations from alcohol.

Commercial samples of 2 : 4-dichlorophenoxyacetic acid, m. p. 146°, methyl 2 : 4-dichlorophenoxyacetate, m. p. 43°, and α-2 : 4-dichlorophenoxypropionic acid, m. p. 117°, were crystallised several times from methyl alcohol.

Methyl and ethyl 3-chloro-4-hydroxybenzoate (m. p.s 106° and 77°, respectively) gave the methyl and ethyl 4-alkoxy-3-chlorobenzoates by the standard methods.

3-Bromo-4-hydroxybenzoic acid, m. p. 156°, was obtained from *p*-hydroxybenzoic acid by the action of bromine in acetic acid; the methyl and ethyl 3-bromo-4-hydroxybenzoates had m. p. 107° and m. p. 102°, respectively. The methyl and ethyl 4-alkoxy-3-bromobenzoates (Table 10) were prepared by alkylation of these esters by standard methods.

5-Chloro-2-hydroxybenzoic acid, m. p. 172°, was prepared by the chlorination of salicylic acid in chloroform with dichloramine-T. The methyl ester melted at 47°, and the ethyl ester at 25°.

Salicylic acid and bromine in acetic acid gave 5-bromo-2-hydroxybenzoic acid, m. p. 165°; methyl ester, m. p. 60°. Alkylation of the 5-chloro- and 5-bromo-esters gave the 2-alkoxy-5-halogenobenzoates.

Most of the remaining ethers (Table 11) were either purchased or were available from previous studies. All were crystallised at least twice from alcohol. 2-Bromo-4-fluoroanisole, b. p. 87°/3 mm., was prepared by adding bromine in acetic acid (8 g. in 50 c.c.) during

TABLE 10. *Physical constants of the ethers* 1 : 2 : 4-RO·C_6H_3XY.

					Found (%)			Reqd. (%)	
X	Y	R	M. p.	B. p./mm.	C	H	Formula	C	H
H	NO_2	Me	52·5°	—	—	—	—	—	—
,,	,,	Et	59	—	—	—	—	—	—
,,	,,	Pr^n	—	126°/2	—	—	—	—	—
,,	,,	Bu^n	32	148/5	—	—	—	—	—
,,	,,	*n*-Amyl	—	147/2	63·3	7·2	$C_{11}H_{15}O_3N$	63·2	7·1
,,	,,	*n*-Octyl	—	219/14	—	—	—	—	—
,,	,,	CH_2Ph	106	—	—	—	—	—	—
NO_2	NO_2	Me	29	229/760	—	—	—	—	—
,,	,,	Et	32	237/760	—	—	—	—	—
,,	,,	Pr^n	—	109/4	52·9	5·0	$C_9H_{10}OCl_2$	52·7	4·9
,,	,,	Pr^i	—	94/2	52·7	5·0	$C_9H_{10}OCl_2$	52·7	4·9
,,	,,	Bu^n	—	121/3	54·7	5·4	$C_{10}H_{12}OCl_2$	54·9	5·5
,,	,,	Bu^i	—	148/12	54·9	5·6	$C_{10}H_{12}OCl_2$	54·9	5·5
,,	,,	*n*-Amyl	—	228/760	57·1	6·0	$C_{11}H_{14}OCl_2$	56·8	6·0
,,	,,	*iso*Amyl	—	157/10	—	—	—	—	—
,,	,,	CH_2Ph	61	—	—	—	—	—	—
Br	Br	Me	61	—	—	—	—	—	—
,,	,,	Et	53	—	—	—	—	—	—
,,	,,	Pr^n	—	140/7	37·0	3·5	$C_9H_{10}OBr_2$	36·8	3·4
,,	,,	Pr^i	—	139/6	—	—	—	—	—
,,	,,	Bu^n	—	169/8	39·1	3·9	$C_{10}H_{12}OBr_2$	38·9	3·9
,,	,,	Bu^i	—	158/5	39·0	3·9	$C_{10}H_{12}OBr_2$	38·9	3·9
,,	,,	*n*-Amyl	—	178/8	40·8	4·2	$C_{11}H_{14}OBr_2$	40·9	4·4
,,	,,	*iso*Amyl	—	182/10	41·1	4·3	$C_{11}H_{14}OBr_2$	40·9	4·4
,,	,,	CH_2Ph	68	—	—	—	—	—	—
Cl	CO_2Me	Me	93	—	—	—	—	—	—
,,	,,	Et	48	168/12	56·3	5·1	$C_{10}H_{11}O_3Cl$	56·0	5·1
,,	,,	Pr^n	—	182/12	58·1	5·7	$C_{11}H_{13}O_3Cl$	57·8	5·7
,,	CO_2Et	Me	76	—	—	—	—	—	—
,,	,,	Et	51	—	—	—	—	—	—
,,	,,	Pr^n	—	179/7	59·3	6·3	$C_{12}H_{15}O_3Cl$	59·3	6·2
,,	,,	Bu^n	—	186/8	60·8	6·6	$C_{13}H_{17}O_3Cl$	60·7	6·6
,,	,,	*n*-Amyl	24	190/7	62·1	6·9	$C_{14}H_{19}O_3Cl$	61·9	7·05
Br	CO_2Me	Me	94	—	44·2	3·7	$C_9H_9O_3Br$	44·1	3·7
,,	,,	Et	46	177/15	46·0	4·1	$C_{10}H_{11}O_3Br$	46·3	4·25
,,	,,	Pr^n	—	192/7	47·3	5·0	$C_{11}H_{13}O_3Br$	48·0	4·8
,,	CO_2Et	Me	73	—	—	—	—	—	—
,,	,,	Et	60	—	—	—	—	—	—
,,	,,	Pr^n	35	179/5	49·8	5·2	$C_{12}H_{15}O_3Br$	50·2	5·2
,,	,,	Bu^n	—	190/8	51·3	5·6	$C_{13}H_{17}O_3Br$	51·7	5·65
,,	,,	*n*-Amyl	28	224/7	53·5	5·9	$C_{14}H_{19}O_3Br$	53·3	6·0
CO_2Me	Cl	Me	—	148/9	—	—	—	—	—
,,	,,	Et	—	156/9	56·5	5·3	$C_{10}H_{11}O_3Cl$	56·0	5·1
,,	Br	Me	38	168/15	—	—	—	—	—
,,	,,	Et	48	160/8	—	—	—	—	—

1 hr. to *p*-fluoroanisole (7 g.; prepared by the Balz–Schiemann method from *p*-anisidine) and powdered sodium acetate (10 g.) in a minimum of glacial acetic acid. 2-Bromo-4-chloroanisole, prepared similarly, had b. p. 95°/2 mm. 4-Bromo-2-chloroanisole was obtained by slowly adding a solution (7 g. in 50 c.c.) of dichloramine-T in acetic acid, with cooling, to *p*-bromoanisole in acetic acid (9·3 g. in 50 c.c.). After 24 hr., the solution was diluted with water and the solid crystallised from methyl alcohol.

TABLE 11. *Miscellaneous phenyl ethers.*

	M. p.	k_{20} (l. mole^{-1} sec.$^{-1}$)
p-Fluorophenoxyacetic acid	106°	9·5
p-Chlorophenoxyacetic acid	157	4·1
p-Bromophenoxyacetic acid	158	5·6
α-*p*-Chlorophenoxypropionic acid	116	5·0
β-*p*-Chlorophenoxypropionic acid	138	38
β-*p*-Bromophenoxypropionic acid	146	51
p-Fluorophenyl *o*-nitrobenzyl ether	62	15·6
p-Chlorophenyl *o*-nitrobenzyl ether	69	9·5
p-Chlorophenyl *p*-nitrobenzyl ether	102	11·7
Benzyl 4-chloro-2-nitro-3 : 5-xylyl ether	105	0·493
2-Bromo-4-fluoroanisole	(b. p. 87°/3 mm.)	0·829
2-Bromo-4-chloroanisole	(b. p. 95°/2 mm.)	0·349
4-Bromo-2-chloroanisole	69	0·296
p-Nitrophenyl *n*-octyl ether	26	0·349

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*The S_N Mechanism in Aromatic Compounds. Part XIV.**

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The rate of replacement of halogen in 1-halogeno-2-nitrobenzenes by methoxide in methanol has been measured. The order F > Cl > Br > I is found, as with 1-halogeno-4-nitro- and 1-halogeno-2 : 4-dinitro-benzenes. The absence of steric factors in determining the order of the halogens is shown, and the *ortho*- and *para*-series are compared.

EARLIER papers [Beckwith, Miller, and (in part) Leahy, *J.*, 1952, 3552; Briner, Miller, and (in part) Liveris and Lutz, *J.*, 1954, 1265] were concerned with the replacement of halogens from aromatic compounds by S_N reactions. The present paper deals with the replacement of the halogens when the sole activating group is an *o*-nitro-group, the reagent being methoxide in absolute methanol as before. The experimental measurements and some derived quantities are given in Tables 1 and 2.

In view of other work by Miller *et al.* now proceeding, in extending variation of the replaced group beyond the halogen series, a group replacement factor (G.R.F.) is now defined, being the ratio of the rate constants for replacement of X in ArX and Cl in ArCl (*i.e.*, ArX/ArCl) at a given temperature. Other quantities already defined, and used here, are the substituent rate factor (S.R.F.) and steric index (S.I.) (Miller, *J.*, 1952, 3550; Miller and Williams, *J.*, 1953, 1475).

Discussion.—The now familiar pattern that fluorine is much more easily replaced than the other halogens in activated S_N reactions in the aromatic series is again shown. Apart from minor variations, discussed below, the pattern of the G.R.F.'s is almost the same in the *o*- as in the *p*-nitro-series. This shows clearly that the main pattern is not steric in origin.

* Part XIII, *J. Org. Chem.*, 1955, **20**, 558.

TABLE 1. *Rate constants, etc., for 1-halogeno-2-nitrobenzenes.*

	Temp.	Rate constant * ($10^5 k_2$; l. mole^{-1} sec.$^{-1}$)	Group replacement factor 0°	50°	100°	E † (cal.)	$\log_{10} B$
F ‡	0°	(0·658)	2210	722	317	19,700	10·4
	45·3	114					
	50·0	(181)					
	60·2	463					
	82·0	2860					
	100·0	($11,0_{50}$)					
Cl	0	(0·000297)	1	1	1	$23,6_{50}$	10·4
	50·0	(0·252)					
	75·3	3·62					
	81·6	6·82					
	100·0	(35·0)					
	100·8	37·4					
Br	0	(0·000121)	0·407	0·702	1·05	$25,5_{50}$	11·5
	50·0	(0·177)					
	81·8	6·23					
	100·0	(36·7)					
	100·1	36·9					
	113·7	123					
I	0	(0·0000429)	0·144	0·330	0·663	26,500	11·9
	50·0	(0·0829)					
	99·3	19·7					
	100·0	(21·1)					
	120·6	136					
	138·6	605					

* Values in parentheses obtained by using the Arrhenius parameters.

† Probable error in E is ± 1%, *i.e.*, approx. ± 200 cal. The fit to a straight line of the $\log_{10} k_2$ against reciprocal temperature plots is indicated by least-squares calculation of the " probable errors " of these plots; and these are in all cases within the figure given.

‡ For a recent similar study of this compound see Bevan and Bye, *J.*, 1954, 3091.

TABLE 2.

	Group replacement factor *ortho*-series 50°	100°	*para*-series 50°	100°	S.I. 50°	100°	Difference of Arrhenius parameters for *ortho*- and *para*-series E	$\log_{10} B$
F	722	317	312	172	1·46	2·00	−1500	$-1·1_4$
Cl	1	1	1	1	3·36	3·66	− 400	−0·8
Br	0·702	1·05	0·745	0·961	4·04	3·35	+ 400	0
I	0·330	0·603	0·361	0·441	3·78	2·67	+1500	+0·5

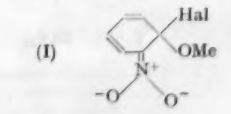
The order of replacement F ≫ Cl > Br > I has been ascribed (*locc. cit.*) to the inductive withdrawal by the halogen of the Ar–Hal bond electrons with consequent facilitation of attack by OMe^- on the ring carbon atom. An attempt was also made to correlate the activation energies with calculated electronegativity and conflicting bond strength factors, the latter being those of the Ar–Hal bonds. It was hoped that this treatment might be extended to the aliphatic series. While this gave fair agreement with experiment, the use of Ar–Hal bond strengths as a factor may not be justified if in the transition state the Ar–Hal bond is not yet broken, but merely changed to a bond of aliphatic type. If they were known, the differences between the Ar–Hal and Aliph–Hal bond strengths might be used. These differences will in any case parallel the C–Hal bond strengths; so both treatments should give similar results.

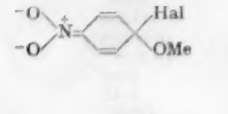
It should be noted that, if the Ar–Hal bond is to any extent weaker than a full bond in the transition state, then solvation of the partially formed halide ion will also favour replacement in the order F > Cl > Br > I, the difference between fluorine and the others being largest.

Another point is that the operation of the $+M$ effect is one of the factors favouring the opposite order to that found experimentally. It operates effectively only in the initial state of the Ar–Hal molecule.

Inasmuch as the bonding of halogen in the transition state is not known, though usually approximated to a full Aliph–Hal bond, it is thought unprofitable at present to attempt further analysis of the activation energies.

The comparatively small differences between the two mononitro-series are significant: the spread of E and $\log_{10} B$ is bigger in the *ortho*-series—6800 and 1·3, compared with 3800 and 0·5$_5$; in comparing the individual E and log B values, there is a smooth transition in going from fluorine (*ortho*-values lower) to iodine (*ortho*-values higher). The structure of the transition states, in line with aromatic S_N reactions, and the discussion by Miller (*Rev. Pure Appl. Chem.*, 1951, **1**, 171), is regarded as approximating to the structures (I)





and (II). The delocalisation energy of (I) might be expected to be greater than that of (II) with its cross-conjugation, though the apparently greater stability of *p*- than of *o*-quinones indicates that this may not be fully justified. In formation of (I) the compressions of the initial state in the *ortho*-series are released to a considerable extent; no such factor applied to the *para*-series. In the *ortho*-series, the nitro-group is not coplanar with the ring in the initial state but can be so in the transition state: reduction in activating power due to absence of coplanarity is therefore not likely to be important. This is confirmed by examination of the steric indices, for while that for the fluoro-compounds is smaller than the others, those for chlorine, bromine, and iodine are approximately equal, and only slightly bigger than that for fluorine.

The various factors above are consistent with the experimental values of E and B.

Comparison of the *o*- and *p*-halogenonitrobenzenes with the 1-halogeno-2:4-dinitrobenzenes shows that the S.R.F.'s of the *o*- and the *p*-nitro-group are not greatly affected by variation of the replaced group when another activating group is already present; the range of S.R.F. for *o*-NO_2 being 1·26 to 9·69 $\times$ 10^5 at 0°, and for *p*-NO_2 from 6·73 $\times$ 10^5 to 1·14 $\times$ 10^6 at 0°.

While the comparative unimportance of steric effects in series where only the one *ortho*-group is present has been shown, a definite steric effect is to be expected when both *ortho*-positions are occupied and this has already been demonstrated for groups *ortho* to chlorine (Miller, *J.*, 1952, 3550; Miller and Williams, *J.*, 1953, 1475).

Experimental

Runs were followed as in Part II (Miller, *J.*, 1952, 3550), except that graphical plots were used for k_2. Runs were made at least in duplicate at each of three temperatures.

Materials.—*o*-Fluoronitrobenzene, prepared from *o*-nitroaniline by the Schiemann reaction, had b. p. 217°/764 mm., 117·5°/34 mm. (lit., 214·6°/761 mm.).

Table 3.

Titration value ...	7·82	8·33	8·70	9·10	9·49	9·77	10·12	10·50
log term	0·3336	3539	3701	3897	4174	4278	4511	4799
Time (min.)	0	4	8	12	16	20	26	32
Titration value ...	10·90	11·33	11·67	12·08	12·45	12·80	14·09	
log term	5149	5595	6043	6634	7341	8209	—	
Time (min.)	40	50	60	75	90	110	∞	

$k_2 = 4{\cdot}59_4 \pm 0{\cdot}03_9 \times 10^{-6}$ l. mole^{-1} sec.$^{-1}$.

o-Chloro- and *o*-bromo-nitrobenzene were commercial products, crystallised to constant m. p. from methanol and aqueous methanol respectively and had m. p. 32·5° (lit., 32°) and 43° (lit., 43°), respectively.

o-Iodonitrobenzene, prepared from *o*-nitroaniline (Ullmann, *Ber.*, 1896, **29**, 1878) and recrystallised from aqueous methanol, had m. p. 50° (lit., 49·5°, 54°).

Table 4.

Temperature	45·3°		60·2°		82·0°	
Rate constants	113	114	115	462	464	2840	2870
($10^6 k_2$)		(av. 114)		(av. 463)		(av. 2860)	

$E = 19{,}6_{40} \pm 30$ cal.

Typical Kinetic Values.—A typical run (for *o*-fluoronitrobenzene at 60·2°) is given as Table 3, while the full set of rate constants for the same compound used for calculation of " probable error " by least squares is given as Table 4.

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*The S_N Mechanism in Aromatic Compounds. Part XV.**

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[Reprint Order No. 6175.]

The substituent effects of *o*- and *p*-methyl and -trifluoromethyl groups in aromatic nucleophilic substitution have been measured and compared. The methyl group is slightly deactivating; the trifluoromethyl group has an activating power approaching that of methoxycarbonyl and trimethylammonium. The modes of action are discussed.

IN Miller's classification (*Rev. Pure Appl. Chem.*, 1951, **1**, 171) of substituents in S_N reactions in the aromatic series, class (iv) refers to groups attached to the ring by uncharged atoms having no unshared electrons. Subsections (*a*) and (*b*) refer to electron-attracting and electron-repelling groups, which cause activation and deactivation respectively at both *ortho*- and *para*-positions. The present paper confirms the general predictions, and gives a quantitative measure of the effect for methyl and trifluoromethyl groups (Downing, Heppolette, and Miller, *Chem. and Ind.*, 1953, 1260).

The rates of replacement by OMe^- in absolute methanol of the chlorine in (i) 4-chloro-3-nitrotoluene, (ii) 2-chloro-5-nitrotoluene, (iii) 1-chloro-2-nitro-4-trifluoromethylbenzene, and (iv) 1-chloro-4-nitro-2-trifluoromethylbenzene have been measured and by comparison

TABLE 1.

Rate constant ($10^5 k_2$ l. mole^{-1} sec.$^{-1}$)

Compd.	Subst.	(*a*) At temp. in parentheses				(*b*) At 0°	At 50°	Calc.: At 100°	At 150°
(v)	*p*-H	3·62 (75·3)	6·82 (81·6)	37·4 (100·8)	—	0·000297	0·252	35·0	151_5
(vi)	*o*-H	8·42 (71·0)	23·5 (81·6)	137 (100·8)	—	0·000890	0·847	128	5910
(i)	*p*-Me	1·42 (81·9)	35·0 (114·0)	158 (131·1)	296 (138·4)	—	0·0299	9·18	723
(ii)	*o*-Me	6·07 (81·9)	31·6 (99·3)	193 (120·6)	769 (138·4)	—	0·187	33·5	1760
(iii)	*p*-CF_3	49·6 (35·4)	80·0 ($40·0_5$)	134 (45·6)	541 (60·2)	0·745	205	12,500	—
(iv)	*o*-CF_3	81·7 (45·3)	342 (59·9)	1350 (75·3)	2290 (81·6)	0·367	131	2690	—

TABLE 2.

Compd.	S.R.F.* 0	50	100	150	S.I. 0	50	100	150	*E* (cal.)	$\log_{10} B$
(i)	1	1	1	1	1	1	1	1	$23,6_{50}$	10·4
(ii)	1	1	1	1					$24,0_{50}$	11·2
(iii)	—	0·119	0·262	0·477	—	0·538	1·00	1·60	27,400	12·0
(iv)	—	0·221	0·262	0·298					$24,8_{50}$	11·1
(v)	2510	813	357	—	6·08	5·25	4·72	—	19,700	10·6
(vi)	413	155	75·7	—					20,600	11·1

* The S.R.F.s for CO_2Me and NMe_3^+ at 0° are 7240 and $10,7_{50}$ respectively (Miller, *J. Amer. Chem. Soc.*, 1954, **76**, 448; Bolto and Miller, unpublished work).

with the rates for *o*- (v) and *p*-chloronitrobenzenes (vi) (Miller, *J.*, 1952, 3550) the substituent rate factors (S.R.F.; Miller, *loc. cit.*) and the steric indices (S.I.; Miller and Williams, *J.*, 1953, 1475) have been calculated. The results are given as Tables 1 and 2.

* Part XIV, preceding paper.

Discussion.—The methyl group is seen to be slightly deactivating in both the *ortho*- and the *para*-position, the difference being almost negligible but somewhat dependent on the temperature. In S_E reactions in the aromatic series the methyl group is fairly activating, but the *p*/*o* ratios of the partial rate factors are always small (close to 1) : thus for nitration of toluene these factors are 58 and 42 for *para*- and *ortho*-positions, giving a *p*/*o* ratio of 1·38 (Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell & Sons Ltd., London, 1953, p. 259). This suggests that in S_N reactions in the aromatic series, both the $+I$ and the $+M$ hyperconjugation of the methyl group are small.

The absence of steric hindrance is noteworthy and has already been demonstrated (Miller and Williams, *J.*, 1953, 1475) even in the more hindered dinitro-series.

Comparison with the S_E reactions suggests that an important part of the activating power of methyl groups in them is due to a hyperconjugative $+E$ effect.

The electron-attracting power of the trifluoromethyl group is seen to be considerable and approaches that for a cationic $-I$ group, *viz.*, NMe_3^+ (Bolto and Miller, *loc. cit.*), and is comparable with that for the $-I-T$ methoxycarbonyl group (Miller, *loc. cit.*). With three fluorine atoms attached to one carbon atom, we expect a powerful $-I$ effect; but this alone would lead to a greater S.R.F. for the *o*-trifluoromethyl group, and a steric index less than 1. Mere size would not be expected to lower the S.R.F. of the *ortho*-group to the extent found experimentally. A partial explanation (cf. Miller and Williams, *loc. cit.*) is the repulsion between the electronegative fluorine atoms and the attacking OMe^-. More important is probably the hyperconjugative $-E$ effect, acting more effectively from the *para*-position. Such an effect has already been postulated for other reactions, and supporting evidence has been given (de la Mare, Hughes, and Ingold, *J.*, 1948, 17; Roberts, Webb, and McElhill, *J. Amer. Chem. Soc.*, 1950, **72**, 408; Smith and Turton, *J.*, 1951, 1701). The Arrhenius parameters support the hyperconjugative $-E$ effect as paramount, since the values are similar to those for the methoxycarbonyl ($-I-T$) group (Miller, *loc. cit.*; Miller and Williams, *J. Amer. Chem. Soc.*, 1954, **76**, 5482); whereas *ortho*-deceleration due to repulsion between electronegative atoms and OMe^- appears to act by an increase in E not counteracted by an increase in B (Miller and Williams, *loc. cit.*); while the $-I$ cationic group acts by a comparatively small decrease in E augmented by a considerable increase in B.

The frequency factors are difficult to classify. For the *p*-H and *p*-CF_3 compounds the values are almost identical; however, both E and log B for *p*-methyl are high. This surprising result seems to be definite in view of the large temperature range (56·5°) and good plot of log k_2 against reciprocal temperature. The values of the frequency factor are slightly higher for the three *ortho*-compounds than for *p*-H and *p*-CF_3, and this may be connected with a more loosely bound transition state caused by small steric factors.

Experimental

The runs were followed as in Part II (Miller, *loc. cit*), except that graphical plots were used for k_2. Runs for each of at least three temperatures were in duplicate. Estimated errors in E are about ±200 cal., the " probable errors " by the method of least squares being less than this.

Materials.—4-Chloro-3-nitrotoluene was prepared from 4-amino-3-nitrotoluene by a Sandmeyer reaction. The redistilled product had b. p. 260°/760 mm., 81—82°/0·5 mm. (lit., 260°/745 mm.).

2-Chloro-5-nitrotoluene, prepared from *N*-acetyl-*o*-toluidine by nitration according to Page and Heasman's method (*J.*, 1923, **123**, 3235), hydrolysis, and a Sandmeyer reaction, and recrystallised from aqueous methanol, had m. p. 42·5° (lit., 42·5°).

1-Chloro-2-nitro-4- and 1-chloro-4-nitro-2-trifluoromethylbenzene were commercial products, having the recorded physical constants (m. p. 25—27°, b. p. 94—95°/10 mm.; b. p. 102—103°/5 mm.).

The only new product is *1-methoxy-2-nitro-4-trifluoromethylbenzene*, m. p. 80° (Found : C, 43·5; H, 3·0. $C_8H_6O_3NF_3$ requires C, 43·45; H, 2·7%).

Typical Kinetic Values.—A typical run (for 1-chloro-2-nitro-4-trifluoromethylbenzene at 35·4°) is given as Table 3, and the rate constants for the same compound used for calculation of " probable error " by least squares are given as Table 4.

TABLE 3.

Titration value ...	8·98	9·40	9·78	10·14	10·45	10·78	11·00	11·56	12·00
log term	0·1744	1824	1903	1987	2065	2153	2219	2400	2569
Time (hr.)	0	½	1	1½	2	2½	3	4	5
Titration value ...	12·38	12·74	13·01	13·27	13·50	13·72	13·90	16·76	
log term	2734	2911	3062	3222	3383	3547	3698	—	
Time (hr.)	6	7	8	9	10	11	12	∞	

$k_2 = 4{\cdot}92_8 \pm 0{\cdot}011 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$

TABLE 4.

Temperature	35·4°		40·0$_5$°		45·6°		60·2°
Rate constants (10^5k_2)	49·3	49·9	79·9	133	135	538	544

$E = 196_{70} \pm 130$ cal.

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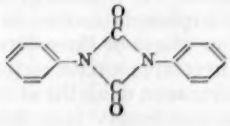
The Crystal Structure of the Phenyl iso*Cyanate Dimer.*

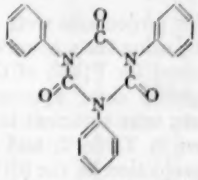
By C. J. BROWN.

[Reprint Order No. 6261.]

The crystal structure of the phenyl *iso*cyanate dimer has been determined from *X*-ray diffraction data. A complete three-dimensional analysis has been carried out, and from the resulting atomic co-ordinates, the geometry of the molecule has been thoroughly investigated. The dimer is found to be isostructural with *p*-terphenyl.

THE dimer and the trimer formed by self-condensation of phenyl *iso*cyanate have long been known (Hofmann, *Annalen*, **1861**, Suppl. **1**, 57), and although their formulæ have been assumed to be (I) and (II) respectively, confirmation by physical methods was desirable. Further, if (I) were correct it would be of interest to determine the bond lengths and inter-bond angles accurately as no similar structure has yet been worked out. The dimensions of the triazine ring in the trimer (II) would be of less interest as these data are already available from compounds such as cyanuric acid (Wiebenga, *J. Amer. Chem. Soc.*, 1952,

(I) 

 (II)

74, 6156), cyanuric triazide (Knaggs, *Proc. Roy. Soc.*, 1935, *A*, **150**, 576), and melamine (Hughes, *J. Amer. Chem. Soc.*, **1941**, **63**, 1737). Accordingly preference was given to the dimer.

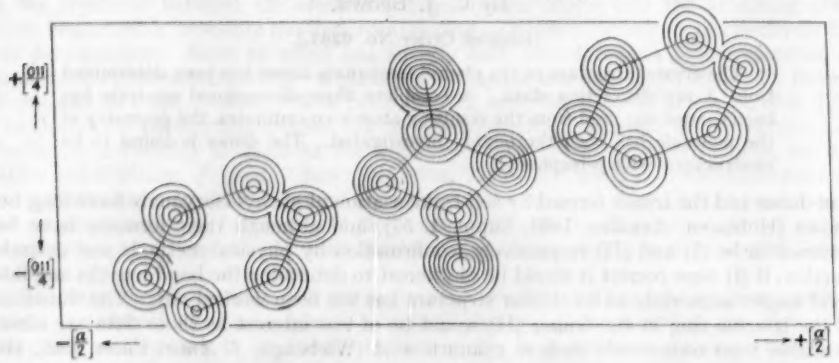
The unit-cell dimensions of the dimer are $a = 12{\cdot}77$, $b = 5{\cdot}50$, $c = 8{\cdot}09$ Å, and the angle $\beta = 92°$. Assuming two molecules per unit cell, and a molecular weight of 238·1 gives 1·393 as calculated specific gravity; that observed by flotation in sodium iodide solution was 1·400. Absent reflexions were $\{0k0\}$ for k odd and $\{h0l\}$ for l odd, so the space group was fixed unambiguously as $P2_1/c$ (C_{2h}^5). This requires that the dimeric molecule shall be centro-symmetrical, and that the centres of the molecules should coincide with the centres of symmetry in the unit cell. The unit cell dimensions of the trimer are $a = 12{\cdot}67$, $b = 13{\cdot}76$, $c = 9{\cdot}83$ Å, and $\beta = 90°$. Absent reflexions indicate body-centering, with space group either Ia or I2/a. The specific gravity of the sample available was rather difficult to determine, the best value being only 1·34 compared with 1·38 required for four

molecules per unit cell. Owing to the large number of atoms, the possible absence of a centre of symmetry, and the size of the unit cell which would preclude the resolution of individual atoms in projection, no further work was done on the trimer.

Determination of the Structure.—The unit-cell dimensions of the dimer bore a close resemblance to those of *p*-terphenyl (Pickett, *Proc. Roy. Soc.*, 1933, *A*, **142**, **333**) and, as the space groups were the same, it was probable that the molecular packing in the two structures would be identical. The way in which organic compounds of similar molecular shape may crystallise in an isostructural series has been noted before (Brown, *Acta Cryst.*, 1951, **4**, 100) and Table 1 shows the crystal data for some of these substances.

In each of these crystals, the two unit-cell dimensions b and c correspond very closely; these are determined by the closest lateral packing of benzene rings. The other dimension a and the angle β depend on the length of the molecule and the nature and size of the *para*-substituents. Use was made of this analogy in the determination of the structure of the phenyl *iso*cyanate dimer. After due allowance for the small difference in length of the molecules, the co-ordinates worked out for *p*-terphenyl (Pickett, *loc. cit.*) were given to the dimer. There was at once moderately good agreement between the calculated and the experimental structure amplitudes for the $h0l$ planes of the highest spacing, and two

FIG. 1. *Composite three-dimensional electron density map represented as a projection on the* (011) *plane. The contours are at intervals of* 1 e/Å^3, *commencing at* 2 e/Å^3. *The origin is at the centre of the molecule.*



stages of Fourier projections were adequate to complete the refinement of this zone. In the same way, by using the y co-ordinates from the *p*-terphenyl structure, satisfactory agreement was obtained for F{hkl} of the dimer, and two stages of three-dimensional Fourier syntheses computed along appropriate lines and over appropriate sections, with finally all the 726 terms, were sufficient to complete the refinement of all the atomic co-ordinates. These are given in Table 2, and a composite electron-density map showing the whole molecule as a projection on the (011) plane is reproduced in Fig. 1.

TABLE 1. *Cell dimensions of some analogous structures.*

	a	b	c	β
Phenyl *iso*cyanate dimer	12·77	5·50	8·09	92°
p-Terphenyl	13·59	5·60	8·08	92°
Diphenyl	9·57	5·67	8·11	94½°
4 : 4′-Diphenyldiphenyl	18·4	5·64	8·14	97°
γ-Quinol	13·24	5·20	8·11	107°

TABLE 2. *Atomic co-ordinates of the dimer.**

	x	y	z		x	y	z		x	y	z
C_1	0·184	Ī·994	0·073	C_4	0·393	Ī·997	0·173	C_7	0·012	0·160	Ī·931
C_2	0·247	0·174	0·021	C_5	0·328	Ī·822	0·228	N	0·078	Ī·991	0·017
C_3	0·352	0·176	0·071	C_6	0·224	Ī·818	0·173	O	0·023	0·330	Ī·850

* For numbering see Fig. 2.

TABLE 3. *Experimental and calculated structure amplitudes.*

hkl	F(exp.)	F(calc.)	*hkl*	F(exp.)	F(calc.)	*hkl*	F(exp.)	F(calc.)	*hkl*	F(exp.)	F(calc.)
100	31	+47	806	7	+ 8	613̄	4	+ 5	10,2,0	8	+10
200	6	− 6	906	3	− 3	513̄	8	−12	11,2,0	7	+ 7
300	51	+50	10,0,8̄	3	− 5	413̄	3	+ 4	13,2,0	5	+ 3
400	17	+16	808̄	2	− 4	313̄	3	+ 2	15,2,0	5	+ 4
500	40	+34	708̄	6	− 9	213̄	17	+20	13,2,1̄	5	− 3
600	11	+10	608̄	5	− 4	113̄	52	+38	12,2,1̄	6	− 5
700	17	−16	508̄	4	− 3	013	15	+11	11,2,1̄	7	+ 8
800	6	+ 7	008̄	7	− 6	113	22	+15	92$\bar{1}$	12	−12
900	8	+11	508	12	−14	213	2	0	82$\bar{1}$	5	+ 6
10,0,0	4	+ 2	608	5	− 5	313	3	+ 3	72$\bar{1}$	8	+10
11,0,0	4	+ 3	708	5	+ 9	413	16	+16	62$\bar{1}$	2	0
12,0,0	7	+11	4,0,1̄0	3	+ 3	513	6	− 6	52$\bar{1}$	5	+ 5
13,0,0	4	+ 4	2,0,10	3	− 3	613	7	− 6	42$\bar{1}$	2	− 2
15,0,0	2	+ 2	3,0,10	2	− 3	713	6	− 5	32$\bar{1}$	11	+ 8
15,0,2̄	3	− 3	4,0,10	4	− 6	813	4	− 2	22$\bar{1}$	22	+23
11,0,2̄	7	+ 6	310	8	−12	913	4	+ 4	021	2	+ 6
10,0,2̄	11	−13	410	8	−12	11,1,3	7	+ 8	121	13	−14
902̄	16	−14	510	10	−11	10,1,4̄	4	− 2	221	3	− 5
802̄	14	−15	610	8	−11	514̄	3	− 5	321	5	+ 2
702̄	18	−18	810	10	−13	414̄	8	+12	421	2	− 3
602̄	5	0	910	13	−19	314̄	12	+16	10,2,1	3	+ 3
502̄	24	−19	12,1,0	7	−12	214̄	12	−19	13,2,2̄	6	+ 6
402̄	18	−11	13,1,0	4	− 5	114̄	6	− 7	12,2,2̄	5	+ 5
302̄	16	−16	13,1,1̄	5	+ 6	014	20	−20	11,2,2̄	7	+ 5
202̄	16	−13	12,1,1̄	4	+ 5	114	5	+ 5	82$\bar{2}$	3	− 2
102̄	83	+74	11,1,1̄	7	+ 9	214	9	+10	72$\bar{2}$	4	− 4
002	33	+23	10,1,1̄	3	+ 3	314	7	+ 6	62$\bar{2}$	9	+ 9
102	20	−17	91$\bar{1}$	3	− 3	414	12	+11	52$\bar{2}$	5	− 6
202	28	+20	81$\bar{1}$	2	− 2	514	6	− 7	42$\bar{2}$	5	− 5
402	38	+25	71$\bar{1}$	8	−12	614	3	+ 3	32$\bar{2}$	10	+ 8
502	17	+13	61$\bar{1}$	3	+ 7	714	19	+22	22$\bar{2}$	7	+ 6
602	21	−17	51$\bar{1}$	3	+ 4	914	4	− 5	12$\bar{2}$	25	+19
702	6	+ 6	41$\bar{1}$	7	− 8	10,1,4	7	+10	022	17	+12
802	20	+18	31$\bar{1}$	5	+ 7	11,1,4	6	+ 6	122	22	+14
902	6	+ 6	21$\bar{1}$	11	−18	12,1,4	3	+ 3	222	9	− 6
10,0,2	7	+ 4	11$\bar{1}$	44	+46	13,1,4	2	+ 3	322	21	−20
11,0,2	16	+21	011	63	+61	81$\bar{5}$	4	− 7	422	2	+ 2
12,0,2	12	+10	111	16	−17	61$\bar{5}$	9	−16	522	11	−10
13,0,2	3	+ 3	211	7	+ 4	51$\bar{5}$	7	−10	622	6	− 6
14,0,2	7	+ 7	311	10	− 9	21$\bar{5}$	7	+ 6	722	14	−13
15,0,2	2	+ 3	411	2	− 4	11$\bar{5}$	7	+ 6	822	25	−26
12,0,4̄	12	+15	511	5	+ 9	015	9	+ 9	922	5	+ 5
11,0,4̄	4	− 7	611	18	−19	115	7	− 7	10,2,2	8	+ 7
10,0,4̄	10	−13	711	11	−12	215	3	+ 3	11,2,2	5	− 5
804̄	6	− 8	811	5	− 5	315	6	+ 6	13,2,2	5	− 4
604̄	11	−10	911	3	− 2	615	9	− 9	15,2,2	3	+ 2
504̄	27	−24	10,1,1	3	+ 4	715	7	− 8	14,2,3̄	3	− 4
204̄	4	− 1	11,1,1	3	+ 3	815	7	+ 8	13,2,3̄	5	− 6
004	9	+ 3	12,1,1	7	+ 7	915	4	+ 3	11,2,3̄	5	− 4
104	9	− 8	13,1,2̄	5	− 6	10,1,5	5	+ 5	10,2,3̄	12	−15
204	26	−23	11,1,2̄	5	+ 9	11,1,5	3	+ 3	923̄	6	− 6
304	8	− 3	10,1,2̄	7	−13	13,1,5	4	+ 5	723̄	8	− 9
404	14	− 9	912̄	7	−13	416	4	− 5	623̄	7	− 8
504	19	−17	812̄	5	+ 7	516	4	− 4	523̄	13	−15
604	13	−12	712̄	3	− 6	616	6	+ 6	423̄	9	−10
704	15	−15	612̄	7	−11	816	6	− 8	323̄	14	+14
804	4	− 3	512̄	9	−15	017	5	− 5	223̄	10	−12
10,0,4	3	+ 3	412̄	20	−30	117	7	− 7	123̄	28	−28
11,0,4	4	+ 5	312̄	5	+ 5	317	5	− 6	023	12	−11
13,0,4	2	+ 2	112̄	76	−61	417	3	− 2	123	8	− 6
13,0,6̄	5	+ 9	012	36	+24	517	7	−10	223	16	+12
11,0,6̄	6	− 8	112	6	− 5	617	10	−14	423	4	+ 4
906̄	3	− 2	212	40	+31	020	5	− 5	523	5	− 4
606̄	10	−14	312	22	+23	220	12	+ 9	623	10	−12
406̄	8	+12	412	20	+17	320	21	−23	723	7	+ 7
206̄	3	+ 2	512	17	+17	420	22	−25	923	11	−11
106̄	18	+19	712	7	+ 8	520	5	− 1	924̄	7	− 7
006	7	+ 7	812	9	+12	620	13	−14	824̄	7	− 7
106	12	−10	12,1,3̄	4	+ 8	720	6	− 4	724	3	+ 5
606	23	−24	10,1,3̄	6	−10	820	11	−12	624̄	3	− 4
706	4	− 4	813̄	5	− 6	920	15	−18	424̄	4	− 2

TABLE 3. (*Continued.*)

hkl	F(exp.)	F (calc.)	*hkl*	F(exp.)	F(calc.)	*hkl*	F(exp.)	F(calc.)	*hkl*	F(exp.)	F(calc.)
$32\bar{4}$	7	− 6	128	3	+ 2	433	7	− 8	$74\bar{1}$	5	− 7
$22\bar{4}$	29	+28	228	5	+ 5	533	12	−11	$64\bar{1}$	2	+ 1
$12\bar{4}$	24	+18	328	3	− 5	633	4	− 3	$54\bar{1}$	2	− 3
024	7	+ 3	428	4	− 4	733	18	−19	$44\bar{1}$	2	+ 2
124	11	+ 9	528	3	− 4	833	11	−12	$34\bar{1}$	2	− 2
224	5	− 4	628	3	− 2	933	11	+10	$24\bar{1}$	5	−12
324	18	+10	728	3	− 3	$43\bar{4}$	3	− 2	141	6	+ 8
424	8	+ 5	928	3	+ 3	$13\bar{4}$	5	− 1	241	4	+ 5
524	5	− 4	$42\bar{6}$	5	+ 7	034	12	+ 5	10,4,1	4	− 4
624	5	− 3	$32\bar{6}$	2	+ 2	134	8	+ 2	13,4,1	3	− 2
724	12	−11	$12\bar{6}$	4	+ 4	234	3	0	11,4,2	3	+ 5
824	4	+ 4	029	4	− 3	334	6	+ 1	$84\bar{2}$	2	− 2
924	8	+ 7	129	4	− 4	434	5	+ 1	$74\bar{2}$	2	− 2
11,2,4	5	+ 4	229	2	− 4	534	6	+ 3	$64\bar{2}$	2	+ 5
$82\bar{5}$	4	− 2	429	2	− 2	634	5	+ 1	$54\bar{2}$	2	− 4
$72\bar{5}$	5	− 4	529	5	− 6	734	5	− 3	$44\bar{2}$	5	− 4
$62\bar{5}$	5	− 7	230	3	+ 1	12,3,$\bar{5}$	4	+ 4	$14\bar{2}$	8	+12
$52\bar{5}$	7	− 7	330	5	+ 3	11,3,$\bar{5}$	6	+ 7	242	3	− 2
$42\bar{5}$	3	− 1	11,3,$\bar{1}$	5	+ 5	10,3,$\bar{5}$	4	+ 4	342	7	− 9
$32\bar{5}$	6	− 7	10,3,$\bar{1}$	3	− 3	$93\bar{5}$	3	− 3	542	4	− 6
$22\bar{5}$	17	−17	$93\bar{1}$	15	−17	$83\bar{5}$	5	+ 5	642	4	− 7
$12\bar{5}$	11	− 7	$83\bar{1}$	6	− 6	$73\bar{5}$	5	+ 6	742	6	− 6
025	10	+ 5	$73\bar{1}$	7	− 8	$63\bar{5}$	3	+ 3	842	7	−12
125	19	+15	$63\bar{1}$	5	− 5	$53\bar{5}$	6	+ 8	10,4,$\bar{3}$	5	+ 9
225	15	+11	$53\bar{1}$	4	− 4	$43\bar{5}$	9	− 9	$74\bar{3}$	2	+ 6
325	18	+13	$43\bar{1}$	20	−22	$33\bar{5}$	9	+ 8	$64\bar{3}$	2	+ 4
425	13	+ 9	$23\bar{1}$	12	+14	$23\bar{5}$	28	+29	$54\bar{3}$	7	+10
625	14	+12	$13\bar{1}$	4	+ 1	135	3	+ 4	$44\bar{3}$	5	+ 7
725	12	+12	031	3	− 1	335	7	+ 7	$34\bar{3}$	5	−10
825	5	− 4	131	15	+20	435	8	− 6	$24\bar{3}$	7	+ 9
10,2,5	7	+ 7	231	10	+10	535	10	−10	$14\bar{3}$	12	+16
$92\bar{6}$	7	− 6	331	14	−18	635	8	− 7	043	8	+ 9
$62\bar{6}$	3	− 2	531	2	+ 1	735	8	− 7	143	8	+ 7
$52\bar{6}$	6	− 5	731	4	+ 6	12,3,5	4	− 4	243	2	− 5
$42\bar{6}$	12	−13	831	20	−21	$43\bar{6}$	5	+ 1	443	2	− 2
$32\bar{6}$	14	+14	931	3	− 4	$33\bar{6}$	7	+ 1	543	6	+ 5
$22\bar{6}$	14	+13	10,3,1	16	+13	336	5	+ 1	643	7	+ 8
$12\bar{6}$	7	− 7	14,3,$\bar{2}$	2	0	436	6	+ 2	743	3	− 5
126	6	− 3	12,3,$\bar{5}$	3	− 1	$83\bar{7}$	5	+ 3	843	3	− 3
226	3	+ 3	11,3,$\bar{2}$	3	− 3	$53\bar{7}$	4	− 4	943	4	+ 7
326	5	+ 5	$93\bar{2}$	3	+ 1	$43\bar{7}$	5	+ 3	$74\bar{4}$	6	+ 4
426	10	− 9	$83\bar{2}$	5	− 3	$33\bar{7}$	20	+21	$24\bar{4}$	12	+14
526	9	− 6	$73\bar{2}$	2	0	$23\bar{7}$	9	+ 6	$14\bar{4}$	7	+ 8
626	5	− 3	$63\bar{2}$	2	0	$13\bar{7}$	5	+ 3	144	4	+ 4
926	3	+ 3	$43\bar{2}$	3	+ 3	037	9	+ 9	344	3	+ 4
10,2,6	6	+ 5	$13\bar{2}$	7	+ 5	137	6	+ 5	544	3	− 3
$72\bar{7}$	3	+ 4	132	9	+ 5	237	16	+13	744	7	− 7
$62\bar{7}$	5	+ 4	232	5	+ 1	337	6	+ 5	$54\bar{5}$	4	+ 4
$52\bar{7}$	3	0	832	7	− 3	437	5	− 4	$34\bar{5}$	6	+ 6
$42\bar{7}$	4	+ 3	932	7	− 2	637	4	+ 5	$24\bar{5}$	9	+11
$32\bar{7}$	8	+ 8	14,3,$\bar{3}$	5	+ 5	937	6	+ 6	145	7	− 8
227	4	+ 1	13,3,$\bar{3}$	7	+ 6	040	5	+ 5	245	6	− 6
327	6	+ 2	$93\bar{3}$	5	− 5	240	2	− 2	345	6	− 7
427	5	+ 2	$83\bar{3}$	9	−11	340	6	− 9	645	8	− 8
527	4	+ 3	$73\bar{3}$	5	− 3	440	6	−12	745	8	− 9
627	5	+ 4	$63\bar{3}$	5	− 4	640	5	− 8	10,4,5	5	− 5
727	2	+ 1	$53\bar{3}$	13	−13	740	6	− 6	$34\bar{6}$	7	+ 7
827	2	+ 2	$43\bar{3}$	9	− 7	840	7	− 7	$24\bar{6}$	7	+ 7
927	3	+ 3	$33\bar{3}$	12	−13	940	5	− 8	046	4	+ 3
10,2,7	2	+ 3	$13\bar{3}$	7	+ 7	13,4,$\bar{1}$	3	+ 3	246	5	+ 1
$52\bar{8}$	4	− 4	033	8	− 7	11,4,$\bar{1}$	7	− 7	346	5	+ 3
$42\bar{8}$	6	+ 6	133	4	− 3	10,4,$\bar{1}$	2	− 1			
$32\bar{8}$	9	+ 9	233	21	−16	$94\bar{1}$	4	+ 7			
$12\bar{8}$	3	+ 3	333	13	−12	$84\bar{1}$	4	− 5			

Description of the Structure.—The crystal structure of the phenyl *iso*cyanate dimer comprises discrete molecules, each of which has a centre of symmetry relating the two halves of the molecule. There is no intermolecular bonding other than van der Waals contacts, of which the closest are O–O′ = 3·23, C_3–C_5' = 3·90, C_2–C_6' = 3·91, C_3–C_4' = 3·98

and C_4–$C_4' = 3{\cdot}98$ Å. The interatomic bond lengths and inter-bond angles calculated from the co-ordinates listed in Table 2 are shown diagrammatically in Fig. 2. By Cruickshank's method (*Acta Cryst.*, 1949, **2**, 65), the mean standard deviation of the position co-ordinates $\sigma = 0{\cdot}010$ Å for the carbon atoms, hence the standard deviation of a bond is 0·014 Å, and the Gaussian probable error is $\pm 0{\cdot}010$ Å for the bond lengths and $\pm 1°$ for the inter-bond angles. The mean C–C bond length in the benzene ring (1·37 Å) is a little, but not significantly, shorter than the usual value (1·385 Å), that for C_1–N agrees with that found in acetanilide (1·426 Å) (Brown and Corbridge, *ibid.*, 1954. **7**, 711), and that for C_7–O is the same as in ethylene carbonate (Brown, *loc. cit.*, p. 92). The two pairs of C_7–N bonds in the central four-membered ring, which might be expected to be equivalent, are different by 0·07 Å, for which no satisfactory explanation can be given. The angles associated with the benzene ring have 120° as their mean value. The other angles approximate to 90° within the four-membered ring, and 135° externally to it.

The molecule as a whole is not planar. The benzene rings are individually planar, the equation of the mean plane through one of them, derived by least squares, and referred to rectangular axes, being

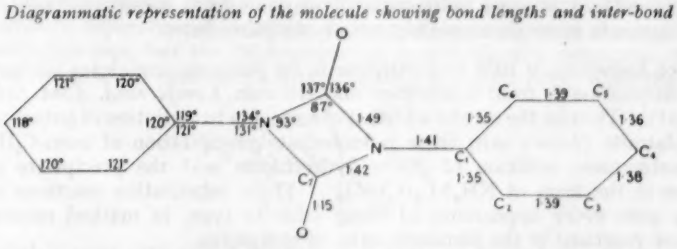
$$0{\cdot}252x' - 0{\cdot}553y - 0{\cdot}794z' = 0{\cdot}135$$

from which the atoms are displaced by the following amounts: C_1 0; C_2 −0·006; C_3 +0·002; C_4 +0·016; C_5 −0·021; C_6 +0·014 Å. The central four-membered ring is necessarily planar, but the C=O bond makes an angle of 87·5° with its normal. The equation of the mean plane through the origin, C_7, N, and O is

$$0{\cdot}088x' - 0{\cdot}555y - 0{\cdot}827z' = 0.$$

The normals to these two planes intersect at an angle of 9·5°. The C_1–N bond makes an angle of 79° with the normal to the central ring, the nitrogen atom being slightly pyramidal. This distortion from planarity may be due to the close approach of the oxygen atom to the benzene ring. If the whole system were rigidly planar, the distances between O and C_2, and between O′ and C_6 would be 3·22 and 3·24 Å respectively, but the distortions

FIG. 2. *Diagrammatic representation of the molecule showing bond lengths and inter-bond angles.*



increase these distances to 3·25 and 3·26 Å. The differences are very slight, but since the true contacts are between the oxygen atoms and the hydrogen atoms attached to the carbon atoms, it may be that in this way adequate clearance is given to the hydrogen atoms.

Experimental

Crystals of the dimer were prepared by Mr. A. C. Farthing of these laboratories by treating phenyl *iso*cyanate with pyridine, and recrystallising the product from benzene. The crystals were mostly platy with (100) tabular, and m. p. 176·2°, although some were acicular with [011] as the needle axis. No good cleavage was observed, but sections of larger crystals were cut to suitable dimensions for *X*-ray photography. The unit-cell dimensions were obtained by measurement of layer lines on rotation photographs. *X*-Ray intensity data were obtained from Weissenberg moving-film photographs about [b] (zero and four layers), and [c] (zero layer only). Multiple films were used for increasing the intensity range, and the densities of the spots were estimated visually by comparison with a time-exposure calibrated film strip. Owing to the platy shape of the crystals, the accuracy of the intensities was not thought to be very

high. After correction for the usual polarisation and geometrical factors, the structure amplitudes were converted to the absolute scale by comparison with calculated values.

The atomic scattering factors used finally were derived experimentally, but corresponded approximately to the values of International Tables, with temperature factor B = 3·5 Å^2.

The precise values were:

$\sin\theta/\lambda$	0	0·1	0·2	0·3	0·4	0·5	0·6	0·7
$4f_c$	24·0	17·0	10·8	7·0	4·6	2·9	1·8	1·3

The residual $R = \frac{\sum|F(exp.) - F(calc.)|}{\sum|F(exp.)|}$ summed over all values of F{*hkl*} except those where F(exp.) = 0 was 0·21. Values of calculated and experimental structure amplitudes are given in Table 3; where F(exp.) = 0, these are omitted, but in these instances the calculated structure amplitudes were all small. No attempt has been made to locate the hydrogen atoms, nor were they allowed for in the structure-amplitude calculations. Neither has any correction been made for errors due to the artificial termination of the Fourier series, but in view of the appreciable temperature factor it is not expected that inaccuracies due to this cause will be very great.

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*The Stability Constants of Some Platinous Halide Complexes.**

By Ido Leden and J. Chatt.

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The equilibria $C_2H_4PtCl_3^- + L \rightleftharpoons$ *trans*-$C_2H_4,LPtCl_2 + Cl^-$ (L = H_2O, Br^-, I^-, and NH_3) are established within 2 min. in aqueous 0·2N-perchloric acid at 25°. Concentration equilibrium constants, *K*, were determined (see Table 1), and the affinities of the halides and thiocyanate ion for platinum shown to lie in the order $F \ll Cl < Br < I < SCN$. For most metals the order of halide stability is $F \gg Cl > Br > I$ and the possible significance of the reversal of order in the case of platinum(II) is discussed. Ammonia relative to water has a very high affinity for platinum(II).

It has been known since 1936 that ethylene in its platinous complexes labilises the group in the *trans*-position to itself (Chernyaev and Hel'man, *Compt. rend. Acad. Sci., U.R.S.S.*, 1936, **4**, 181). Thus on the careful addition of ammonia to a solution of potassium ethylenetrichloroplatinite (Zeise's salt) there is immediate precipitation of *trans*-C_2H_4,NH_3PtCl_2, and on subsequent addition of dilute hydrochloric acid the precipitate immediately redissolves in the form of $NH_4^+ C_2H_4PtCl_3^-$. These substitution reactions are so rapid that they give every appearance of being ionic in type, in marked contrast to most substitution reactions in the platinous series of complexes.

It was of interest therefore to determine whether the ethylenetrichloroplatinite ion undergoes appreciable ionic dissociation in aqueous solution, and how rapidly equilibrium is established. By using silver–silver chloride electrodes to determine the chloride-ion concentration we find that in aqueous 0·2N-perchloric acid the equilibrium

$$C_2H_4PtCl_3^- + H_2O \rightleftharpoons \textit{trans}\text{-}C_2H_4,H_2OPtCl_2 + Cl^-$$

is established in the 2 minutes necessary to prepare the solution. Dissociation of the one chloride ion is practically complete in a 10^{-3}M-solution of $C_2H_4PtCl_3^-$. Thus $C_2H_4PtCl_3^-$ behaves as a labile complex so far as one chlorine atom, presumably that in the *trans*-position to the ethylene molecule, is concerned. This lability has enabled us to determine the relative tendency of the halide and thiocyanate ions to complex formation with platinum(II), by using silver–silver halide or silver–silver thiocyanate electrodes. The use of a compound such as $K^+ C_2H_4PtCl_3^-$, which has essentially the same structure as other

* Throughout this paper square brackets normally used to enclose Werner complexes have been omitted to avoid confusion with square brackets used as a symbol for concentration.

platinous complexes (Chatt and Duncanson, *J.*, 1953, 2939) yet contains a labile chlorine atom, allows the measurement of stability constants to be extended to metals in that region of the Periodic Table where co-ordination compounds are characteristically inert. This is important because the quantitative information on complex stability which is now available relates only to metals whose characteristic complexes are labile.

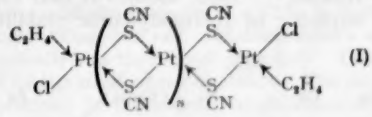
Potassium ethylenetrichloroplatinite undergoes auto-reduction to the metal in neutral or alkaline aqueous solutions but is stable indefinitely in dilute hydrochloric acid solution. These facts, and the knowledge that the *trans*-chlorine atom is labile, indicate that the unstable species in the aqueous solution is probably *trans*-$C_2H_4PtCl_2,OH^-$ formed by the acid dissociation of *trans*-C_2H_4,H_2OPtCl_2.

From the acidity of an aqueous solution of $K^+ C_2H_4PtCl_3^-$ we estimated the acid dissociation constant of the aqua-complex to be of the order 10^{-5}. Since we could not make our equilibrium measurements in presence of a large excess of chloride ion we used 0·2N-perchloric acid to stabilise the ethylene complex and maintain the ionic strength of the reaction medium at about 0·2. In this medium the concentration of hydroxy-complex would be about 0·005% of that of the aqua-complex, and no detectable decomposition of the ethylene complex occurs within a week of preparing the solutions.

The equilibria examined in the perchloric acid solutions were all of the type :

$$C_2H_4PtCl_3^- + L \rightleftharpoons \textit{trans}\text{-}C_2H_4,LPtCl_2 + Cl^- \quad . \quad . \quad . \quad . \quad (1)$$

The equilibrium constants, concentration constants valid at ionic strength 0·2 ($HClO_4$) and 25°, were obtained by determining the concentrations of free L or Cl^- electrometrically. The accuracy of the determinations is limited by slight interference of the platinum salt with the functioning of the electrodes and also, when L is Br^- and I^-, by the occurrence of comparatively slow reactions following the instantaneously established equilibria. These side reactions are probably the replacement of the remaining chlorine atoms or of the ethylene by L. When L = Br^- the interfering reactions are very slow; when L = I^- they are faster but a reasonable constant could still be obtained. When L = SCN^- no constant could be obtained, but only the information that the thiocyanate is taken from the solution into the complex much more avidly than either Br^- or I^-. The side reactions led to the ultimate separation of indefinite decomposition products in the equilibria with bromide and iodide ions, but the thiocyanate ion caused the slow separation of a yellow precipitate of composition close to $(C_2H_4)_2Cl_2(SCN)_{10}Pt_6$. This could have the structure



(I)

(I) ($n = 4$) but is more probably a mixture of substances of that general type or else a mixture of the simplest member ($n = 0$) with $Pt(SCN)_2$. The constants, K, which were determined are :

$$K_{aq.} = [\textit{trans}\text{-}C_2H_4,H_2OPtCl_2][Cl^-][C_2H_4PtCl_3^-]^{-1}$$
$$K_{Br} = [\textit{trans}\text{-}C_2H_4PtBr,Cl_2^-][Cl^-][Br^-]^{-1}[C_2H_4PtCl_3^-]^{-1}$$

and similarly K_I, K_{NH_3}, and K_P.

These are listed in Table 1, together with the equilibrium constants, K_s, referring to the following reaction of formation of the complexes from the aqua-ion in aqueous 0·2N-perchloric acid solution at 25° :

$$\textit{trans}\text{-}C_2H_4,H_2OPtCl_2 + L \rightleftharpoons \textit{trans}\text{-}C_2H_4,LPtCl_2 + aq. \quad . \quad . \quad . \quad (2)$$

The latter are the fourth formation or stability constants which would be obtained if *trans*-$C_2H_4,LPtCl_2$ could be formed stepwise from the aquated Pt^{++} ion, and the ligand L were the last to enter the complex. They are listed together with log K_s for comparison

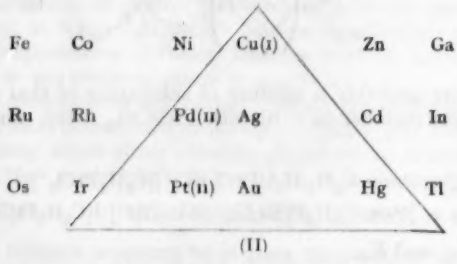
with stability-constant data which are already available in the chemical literature for other metals (*e.g.*, J. Bjerrum, *Chem. Rev.*, 1950, **46**, 381).

TABLE 1. *Constants K and K_s referring to equilibria* (1) *and* (2) *respectively in aqueous* 0·2N-$HClO_4$ *at* 25°.

L	K	K_s	log K_s	L	K	K_s	log K
H_2O	$(3{\cdot}0 \pm 0{\cdot}5) \times 10^{-3}$	(1)	0	I^-	120 ± 20	$4{\cdot}0 \times 10^4$	4·60
F^-	<0·03	<10	<1	NH_3	$\sim 10^5$	-3×10^7	~7·5
Cl^-	(1)	$3{\cdot}3 \times 10^3$	2·52	SCN^-	>120	$>4 \times 10^4$	>4·6
Br^-	$3{\cdot}4 \pm 0{\cdot}3$	$1{\cdot}1 \times 10^3$	3·04				

On making this comparison, it will be noted that as fourth stability constants they are exceptionally high. However, in comparison with average stability constants, they are high but not exceptional; those of Hg(II) ($N = 2$) are all greater. (The average stability constant is the Nth root of the product of the consecutive stability constants up to the last strongly bound ligand, which is the Nth ligand attached to the metal.)

As a rule, the order of thermodynamic stability of the halide complexes of metals which form labile complexes is $F \gg Cl > Br > I$ in aqueous solution, but it has been noted by a number of workers (Carleson and Irving, *J.*, 1954, 4390; Leden, Diss., Lund, 1943, p. 27; J. Bjerrum, *loc. cit.*; Ahrland and Larsson, *Acta Chem. Scand.*, 1954, **8**, 354) that a very small group of elements, copper(I), silver(I), cadmium(II), and mercury(II) have the opposite sequence of stabilities, *viz.*, $F \ll Cl < Br < I$. It is obvious that platinum(II) belongs to this latter group. In this group of metals the great stability of the chloro-complexes relative to the fluoro-complexes has its analogy in the qualitatively observed much greater stability of thio-ether complexes relative to ether complexes, and trialkylphosphine complexes relative to trialkylamine complexes. It is to be noted that all the metals of this group have low valencies yet tend to form strongly covalent complexes with donor atoms of low electronegativity. The increase in stability of the halides as the difference in electronegativity between the metal and halogen falls is evidence of the essentially covalent character of the metal-to-halogen bond. The metals in this group also have filled *d*-orbitals immediately under their valency shells. Chlorine, bromine, and iodine but not fluorine have vacant *d*-orbitals in their valency shells and so dative π-bonding might occur with all except fluorine. These facts may account for the abnormal sequence of stabilities of the halide complexes of the above metals in a way similar to that suggested to explain the greater stability of the phosphine relative to the amine complexes of platinum(II) (Chatt and Wilkins, *J.*, 1952, 4300). If that explanation be true, then the reversal in the normal sequence of thermodynamic stabilities of the common halide



complexes in water should be most marked in the triangle of elements (II) in the Periodic Table which form olefin complexes in their usual valency states, and change over to the normal sequence in the elements bordering on this triangle. This is certainly true of the series of ions Ag^+, Cd^{++}, and In^{+++} (see Carleson and Irving, *loc. cit.*).

It is interesting to speculate on what would be the effect on the platinous halide equilibria of replacing the olefin in the complex ion by ammonia. It is known that the chlorine atom in the *trans*-position to ammonia is not labile, but work at present in progress indicates indirectly that the effect on the position of equilibrium, if equilibrium could be

established, should be slight. The replacement of ethylene by ammonia will not alter the sequence of halide stabilities; rather, we expect that the "abnormal" order may be slightly more pronounced.

Experimental

Microanalyses are by Messrs. W. Brown and A. G. Olney of these laboratories.

Materials.—The acids ($HClO_4$, HCl, HBr, and HI) were of "AnalaR" grade diluted to provide 0·2N-stock solutions, and standardised against 0·1N-potassium hydroxide. Zeise's salt, $K^+C_2H_4PtCl_3^-,H_2O$ was prepared according to Chatt and Duncanson (*J.*, **1953**, 2939), and recrystallised from 0·2N-hydrochloric acid to remove potassium chloride and then from ethanol. The crystals were finally dried *in vacuo* over concentrated sulphuric acid and potassium hydroxide pellets. The infrared spectrum of the solid showed that the material was not anhydrous, but the remaining crystal water was negligible (Found: C, 6·5; H, 1·3; Cl, 28·6; Pt, 52·2. Calc. for $C_2H_4Cl_3KPt$: C, 6·5; H, 1·1; Cl, 28·8; Pt, 52·9%). The quinhydrone (QH) was of "AnalaR" grade. Ammonium perchlorate was dried at 120° and made up to a 0·2M-solution which had **pH 4·96**. Sodium thiocyanate dihydrate was also used in 0·2M-solution whose concentration was determined by silver nitrate titration with fluorescein indicator.

Symbols.—The following symbols are used in the Tables and mathematical equations:

$Z = C_2H_4PtCl_3^-$ $Z_{Br} = trans\text{-}C_2H_4PtBr,Cl_2^-$

$Z_{aq.} = trans\text{-}C_2H_4,H_2OPtCl_2$ Z_I, Z_F, Z_{SCN}, and Z_{NH_3} similarly

C_Z, C_{HCl}, etc. = initial molar concentration of ethylene complex, hydrochloric acid, etc.

e = the e.m.f. of an electrolytic cell (in mv)

E = the change in the e.m.f. of a cell (in mv) on addition of $C_2H_4PtCl_3^-$.

All concentrations are in molarities (M) or normalities (N) at 25°.

Aquation of $C_2H_4PtCl_3^-$: $C_2H_4PtCl_3^- + H_2O \rightleftharpoons trans\text{-}C_2H_4H_2OPtCl_2 + Cl^-$.—The equilibrium constant ($K_{aq.}$) for this reaction was determined by measuring the e.m.f. of the following cell at 25°:

+ Au,QH	0·2N-$HClO_4$	$K^+C_2H_4PtCl_3^-$ (C_Z) HCl (C_{HCl}) $HClO_4$ (0·2 − C_{HCl})	Ag,AgCl −

Silver–silver chloride electrodes. These (2·5 cm. long) were prepared as recommended by Brown (*J. Amer. Chem. Soc.*, **1934**, **56**, 646) on 1·4-mm. diameter platinum wire. The cell was checked without any Zeise's salt but with various amounts of hydrochloric acid to show that the e.m.f. obeyed Nernst's law at 25°, $e = e_0 + 59{\cdot}16 \log [Cl^-]$. The constant e_0 was determined (421·5), and the stock perchloric acid shown to be 3×10^{-5}M in hydrochloric acid, which was allowed for in the experiments. When the cell contained Zeise's salt its potential was not constant, but drifted slowly (usually less than 1 mv per min.). This was probably due to the reduction of the platinous salt by the silver of the electrode. The drift was minimised by using rather large, well-coated electrodes. In the absence of platinous salts the electrodes reached equilibrium, to within 1 mv, with the solutions within 30 sec., usually within 15 sec. The e.m.f. of the cell was therefore measured every minute, for 5 min. from the immersion of the electrode, and extrapolated to zero time. Typical examples are (time in min.; e.m.f. in mv): (*a*) (1; 256·7) (2; 256·5) (3; 256·2) (4; 256·0) (5; 255·8) extrapolated to $e = 257$; (*b*) (1; 280·5) (2; 279·9) (3; 279·1) (4; 278·3) (5; 277·7) extrapolated to $e = 281$. The most rapid shift in all the experiments recorded in this paper was (1; 300·7) (2; 297·5) (3; 294·5) (4; 292·3) extrapolated to $e = 304$. The drift in the e.m.f. of the cell was not very reproducible with different electrodes, but in general it was greater the higher the concentration of Zeise's salt. After the 5-min. period of immersion in presence of platinous salt, the silver–silver chloride electrode was noticeably more sluggish in response to a change in chloride-ion concentration, even in a fresh solution containing no platinum, and so a new electrode was used for every determination. This procedure was checked by confirming that the electrode potential in a solution containing $C_2H_4PtCl_3^-$, and sufficient hydrochloric acid to suppress its dissociation entirely, obeyed Nernst's law on dilution with 0·2N-perchloric acid. We consider that the extrapolation procedure gave us the true "chloride" potential of the cell to within ±2 mv.

Stability of Zeise's Salt in 0·2N-Perchloric Acid.—Although the e.m.f. of the cell was normally measured as soon as the Zeise's salt solutions had been prepared, some solutions were examined at intervals and the e.m.f. was found to be constant, to within experimental error, over a period

of two days. As a typical example we kept a solution of 10^{-2}M-$K^+ C_2H_4PtCl_3^-$ in 0·2N-perchloric acid at 25° for 8 days, then measured the e.m.f. of the cell containing it. The e.m.f. was 283 mv, as compared with 281 and 279 mv for two freshly prepared, but otherwise identical, solutions. Most of the solutions were kept, and after 14 days traces of platinum or other decomposition products were obvious. After 6 weeks some of the solutions had decomposed completely and all showed signs of considerable decomposition.

Determination of the Equilibrium Constant, $K_{aq.}$.—The solutions were prepared by adding known (pipetted) volumes of the acids to a weighed amount of $K^+ C_2H_4PtCl_3^-$ at 25° in the appropriate cell compartment. When dissolution and mixing were complete (2 min.) the electrodes were introduced and the potential of the cell determined as described above. The most dilute solutions were obtained by diluting the more concentrated ones with 0·2N-perchloric acid. The results are given in Table 2: $K_{aq.} = ([Cl^-] - C_{HCl})[Cl^-](C_Z + C_{HCl} - [Cl^-])^{-1}$. Obviously a maximum of one chlorine atom of Zeise's salt dissociates reversibly from the complex ion in solution.

Approximate Determination of the Acid Strength of trans-$C_2H_4.H_2OPtCl_2$.—A solution of Zeise's salt in water is slightly acid and a 0·04M-solution has a pH of about 3·5 (universal indicator paper). Since about 25% of the salt would be in the form of the aqua-complex it follows that the latter has an acid dissociation constant of about 10^{-5}.

Equilibrium between $C_2H_4PtCl_3^-$ and Bromide Ions.—When $K^+ C_2H_4PtCl_3^-$ is added to a solution containing bromide ions, the bromide-ion concentration is immediately reduced owing to the formation of *trans*-$C_2H_4PtBrCl_2^-$. The equilibrium:

$$C_2H_4PtCl_3^- + Br^- \rightleftharpoons \textit{trans}\text{-}C_2H_4PtBrCl_2^- + Cl^- \quad . \quad . \quad . \quad . \quad (3)$$

was therefore examined at 25°, by using the cell:

+ Au,QH	0·2N-$HClO_4$	$K^+ C_2H_4PtCl_3^-$ (C_Z) HCl (C_{HCl}) HBr (C_{HBr}) $HClO_4$ (0·2 − C_{HCl} − C_{HBr})	Ag,AgBr −

The silver–silver bromide electrodes were prepared in the same way as the silver–silver chloride electrodes. They also underwent slow poisoning by the platinous salt, and the extrapolation procedure was used, as previously.

The potential of the cell at 25° was first determined without Zeise's salt. A known quantity of the bromide solution (usually 2 c.c.) was then pipetted into a small tube containing a weighed

TABLE 2. *Equilibrium constant ($K_{aq.}$) for the aquation of $C_2H_4PtCl_3^-$ at 25° and ionic strength 0·2.*

10^3C_Z	10^3C_{HCl}	e	$10^3[Cl^-]$	$10^3K_{aq.}$	10^3C_Z	10^3C_{HCl}	e	$10^3[Cl^-]$	$10^3K_{aq.}$
10	10	310	13·1	(6)	2	0·03	251	1·3	2·4
40	0·03	304	10·4	3·6	2	0·03	253	1·4	3·3
20	0·03	292	6·5	3·1	1	1·03	257	$1·6_7$	3·0
10	0·03	279	3·9	2·5	1	0·03	240	$0·8_6$	(4)
10	0·03	281	4·2	3·0	0·5	0·03	227	$0·5_1$	—
5	0·03	270	2·7	3·2	0·1	0·13	206	$0·2_3$	—

TABLE 3. *The constant, K_{Br}, for equilibrium (3) at 25° and ionic strength 0·2.*

Solution	10^3C_Z	10^3C_{HCl}	10^3C_{HBr}	E	$10^3[Br^-]$	$10^3[Z_{Br}]$	$10^3[Cl^-]$	$10^3[Z]$	K_{Br}
B1	20	0	10	36·7	2·4	7·6	10·4	9·6	3·4
B2	20	0	1	58	0·11	0·89	6·8	13·2	4·1
B3	20	0	40	12·5	24	16	16·6	3·4	3·2
B4	10	10	5	22·4	2·1	2·9	14	6	3·2
B5	5	10	5	12·5	3·1	1·9	12·5	2·5	3·1

quantity of Zeise's salt. When dissolution and mixing were complete (2 min.) the electrode and bridge from the quinhydrone half-cell were quickly transferred from the first cell into the small tube, and the potential noted. The difference (E) between the two potentials gives the bromide concentration directly: $E = 59·16$ (log C_{HBr} − log $[Br^-]$). This technique has the advantage that the effect of any interference of chloride ion with the silver–silver bromide electrode is minimised. It is necessary to measure the potential as soon as possible after the addition of Zeise's salt because, in addition to the immediate decrease in bromide-ion concentration on adding Zeise's salt to the solution, there is a further slow removal of bromide ion

from the solution. If we assume that the immediate removal of bromide ion is caused by the establishment of the above equilibrium, then $K_{Br} = [Z_{Br}][Cl^-][Z]^{-1}[Br^-]^{-1}$ should be constant when the concentrations refer to the metastable equilibrium obtained immediately after mixing. If $K_{aq.}$ is known, the quantities in the above equation can be determined from the equations :

$$[Z_{aq.}] = K_{aq.}[Z][Cl^-]^{-1} \qquad C_{HCl} = [Z] + [Cl^-] - C_Z$$
$$C_Z = [Z] + [Z_{Br}] + [Z_{aq.}] \qquad C_{HBr} = [Z_{Br}] + [Br^-]$$

C_Z, C_{HCl}, and C_{HBr} are all known from the composition of the solution and $[Br^-]$ from the values of E. Solving these equations for $[Cl^-]$ we find

$$2[Cl^-] = C_{HCl} + C_{HBr} - [Br^-] - K_{aq.} + \{(C_{HCl} + C_{HBr} - [Br^-] - K_{aq.})^2 + 4K_{aq.}(C_{HCl} + C_Z)\}^{\frac{1}{2}}$$

and hence K_{Br}. The values of K_{Br} are listed in Table 3. Although $[Br^-]$ and $[Z_{Br}]$ vary widely, K_{Br} is constant to within experimental error, confirming that the instantaneous removal of bromide ion from solution is due to reversible exchange of a chlorine atom in the complex ion for a bromide ion in the solution. The further slow removal of bromide ion from solution is probably due to slow replacement of the ethylene or a *cis*-chlorine atom by bromine. This reaction was followed for a period of up to 27 hr. in the above solutions, as recorded in Table 4; but it is accompanied by decomposition and was not further investigated.

Equilibrium between $C_2H_4PtCl_3^-$ *and Iodide Ions.*—This equilibrium was studied with silver–silver iodide electrodes in analogous manner to the corresponding bromide equilibrium. The solutions were kept in a nitrogen atmosphere to prevent oxidation with liberation of iodine. The first instantaneous reaction was followed by a more rapid slow reaction than in the case of the bromide solutions, leading to a fairly rapid decomposition of the complex. Table 5 lists the results.

Decomposition of the solutions I1 to I5 was as follows: (I1) obvious decomposition after 5 min. (I2) no visible decomposition after 20 min.; colloidal suspension after 1 hr.; $E = 76$ mv after 77 min.; a precipitate collected at the bottom of the container after 3 hr. (I3) completely decomposed in 16 hr. (I4) $E = 26$ mv after 88 min.; 31 mv after 169 min.; no Tyndall effect in 2 hr.; completely decomposed in 20 hr. (I5) decomposed after 2 hr.

TABLE 4. *The change, with time, of the e.m.f.'s of cells containing bromide ion and Zeise's salt at 25°.*

B1		B2		B3		B4		B5	
Time	E	Time	E	Time	E	Time	E	Time	E
2 min.	36·4	3 min.	58	5 min.	12·5	6 min.	22·4	5 min.	12·5
7·0 hr.	73	27·3 hr.	77	1·0 hr.	14	51 min.	22·7	1·8 hr.	14
27·0 hr.*	76			19·7 hr.	35	7·0 hr.	39	3·8 hr.	15
				27·5 hr.	36 †	16·8 hr.	47	22·0 hr.	30
						23·7 hr.	50		

* Decomposition had started.
† This solution had initially a high concentration of bromide ion and on an average the complex ion had absorbed 1·5 bromide ions after 27·5 hr.

TABLE 5. *The constant,* K_I, *at 25° and ionic strength 0·2 for the equilibrium,* $C_2H_4PtCl_3^- + I^- \rightleftharpoons$ *trans*-$C_2H_4PtCl_2I^- + Cl^-$.

Solution	10^3C_Z	10^3C_{HCl}	10^3C_{HI}	E	$10^3[I^-]$	$10^3[Z_I]$	$10^3[Cl^-]$	$10^3[Z]$	K_I
I1	20	0	10	133	0·056	10	12	8	(270)
I2	10	100	5	48·5	0·75	4·25	104	5·5	110
I3	6	180	4	30	1·2	2·8	183	3·2	130
I4	2	184	3·2	12	2·0	1·2	185	0·8	140
I5	7·5	195	1	40	0·21	0·79	196	6·6	110
I6	2	40	1·6	28	0·54	1·06	41	0·84	100

TABLE 6. *Reaction of* $C_2H_4PtCl_3^-$ *with thiocyanate ion at 25° and ionic strength 0·2.*

Solution	10^3C_Z	$10^3C_{SCN^-}$	10^3C_{HCl}	E	$10^3[SCN^-]$	Solution	10^3C_Z	$10^3C_{SCN^-}$	10^3C_{HCl}	E	$10^3[SCN^-]$
T1	20	20	9	100	0·41	T3	6	4	196	49	0·6
T2	10	5	152	61	0·46	T4	3	4	196	30	1·2

Equilibrium between $C_2H_4PtCl_3^-$ *and Fluoride Ions.*—This equilibrium was examined by using the same electrolytic cell as was used in the aquation experiments, but the reaction vessel was made of Polythene, and glass tubes supporting the electrodes were covered with paraffin

wax. The e.m.f. of the cell containing $C_Z = 0{\cdot}4$, $C_{HCl} = 0$, and $C_{HClO_4} = 0{\cdot}2$M was determined (303 mv) and then 40% hydrofluoric acid was added to make the solution about 2N in this acid. The potential of the cell (with a fresh silver chloride electrode) was now 304 mv, which is unchanged to within experimental error. If the reaction :

$$C_2H_4PtCl_3^- + F^- \longrightarrow C_2H_4PtCl_3,F^- + Cl^-$$

occurs it must change the chloride-ion concentration by less than 10% which would correspond to 2·5 mv change in e.m.f. and be outside experimental error. Since the dissociation constant of hydrofluoric acid is about 10^{-3}, the above solution must be about 0·01M in fluoride ion. Hence it follows that the equilibrium constant, $K_F = [Z_F][Cl^-][Z]^{-1}[F^-]^{-1}$, must be less than 0·03.

Reaction between Zeise's Salt and Sodium Thiocyanate.—Attempts to investigate an equilibrium corresponding to those with halide ions by using the silver–silver thiocyanate electrodes were not successful. The thiocyanate ion was avidly taken up by the platinum complex; hence measurements were attempted in presence of relatively large quantities of chloride ion with the results listed in Table 6. Calculation of $K_{SCN} = [Z_{SCN}][Cl^-][Z]^{-1}[SCN^-]^{-1}$ gave values ranging from 300 to 4000. The behaviour of solution T4 in which the thiocyanate ions were in greater molar concentration than $C_2H_4PtCl_3^-$ seems to indicate that only one thiocyanate ion immediately enters the complex ion. It is also evident that the platinum has a much greater affinity for thiocyanate than for iodide ions. Lack of success in obtaining a constant may have been caused by all or any one of the following : (*a*) the slower response of the silver–silver thiocyanate electrode than of the silver–silver halide electrodes (on the other hand the drift in presence of platinous salt was less than with the halide electrodes); (*b*) interference with the electrode by the comparatively high chloride-ion as compared with the thiocyanate-ion concentrations in the solution; (*c*) more rapid subsequent reactions than in the halide system. In solution T1 a Tyndall effect developed within 5 min. and from all solutions a yellow precipitate had formed after 24 hr. This precipitate was stable in contact with the 0·2N-perchloric acid solution for several weeks, and estimation of the halide (Mohr's titration) in the supernatant solution indicated that the thiocyanate had been replaced by about twice its equivalent of halide ion.

The nature of the precipitate was examined by adding 2·20 mmoles of sodium thiocyanate (0·2M) to 2·00 mmoles of $K^+ C_2H_4PtCl_3^-$ in 0·2N-perchloric acid (100 c.c.). The yellow precipitate formed during two days was filtered off, washed with 0·2N-perchloric acid, and then with a little water, and dried; weight 0·403 g. (Found : C, 9·0; H, 0·7; N, 7·7; S, 16·8%). It dissolved in aqueous potassium cyanide with effervescence, indicating the probable presence of ethylene. The filtrate from the yellow precipitate contained no thiocyanate, 0·69 mmole of platinum, and 5·5 mmole of chlorine, indicating an approximate analysis of Pt, 63·5; Cl, 4·(4)%, and ratio SCN : Pt = 1·68 for the precipitate. The analysis is in very close agreement with structure (I) ($n = 4$), *i.e.*, $C_{14}H_8N_{10}Cl_2S_{10}Pt_6$ which requires Cl, 3·8; S, 17·1; Pt, 62·3%; SCN : Pt = 1·67.

Equilibrium between $C_2H_4PtCl_3^-$ *and Ammonia.*—When Zeise's salt is added to a solution of ammonium perchlorate or chloride, the solution becomes strongly acid :

$$NH_4^+ + C_2H_4PtCl_3^- \rightleftharpoons \textit{trans}\text{-}C_2H_4,NH_3PtCl_2 + Cl^- + H^+ \quad . \quad . \quad . \quad (4)$$

By using indicator paper to determine pH, an approximate value of the equilibrium constant, K_{NH_4}, of reaction (4) was obtained (Table 7A). That chloride ion is also liberated on adding Zeise's salt to ammonium perchlorate was demonstrated by measuring the e.m.f. of the following cell :

− Ag,AgCl	HCl (0·01N) / NH_4ClO_4 (0·19M)	$K^+ C_2H_4PtCl_3^-$ (C_Z) / NH_4ClO_4 (0·2M)	Ag,AgCl +

From the chloride-ion concentration K_{NH_4} was also calculated (Table 7B).

TABLE 7. *The constant,* K_{NH_4}, *for equilibrium* (4) *at* 25° *and ionic strength* 0·2.

A				B		
10^3C_Z	NH_4^+ salt (0·2M)	pH	pK_{NH_4}	ε	$10^3[Cl^-]$	pK_{NH_4}
40	NH_4ClO_4	2·0	3·5	+ 9	14·4	3·5
10	NH_4ClO_4	2·4	4	−11	6·5	3·6
40	NH_4Cl	2·7	4			

Since pK_{NH_3} is approximately 4 and the acid dissociation of the ammonium ion about 10^{-9} (J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," Haase and Son, Copenhagen, 1941, p. 290), it follows that the equilibrium constant K_{NH_3} for reaction (5) is about 10^5.

$$C_2H_4PtCl_3^- + NH_3 \rightleftharpoons trans\text{-}NH_3,C_2H_4PtCl_2 + Cl^- \quad . \quad . \quad . \quad . \quad (5)$$

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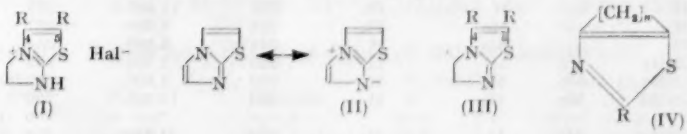
4′ : 5′-*Dihydroglyoxalino*(2′ : 1′-2 : 3)*thiazolium Salts, and the Ultraviolet Light Absorption of Thiazole Derivatives.*

By WALTER WILSON and R. WOODGER.

[Reprint Order No. 6290.]

Tetrahydro-2-thioglyoxaline with α-halogenated carbonyl compounds readily affords 4′ : 5′-dihydroglyoxalino(2′ : 1′-2 : 3)thiazolium salts, which are converted by alkali into bicyclic bases of the 2-iminothiazoline type. The ultraviolet light absorption properties of a number of thiazole derivatives are described. 2-Aminothiazoles and 2-iminothiazolines absorb similarly; the higher dipole moments of the latter indicate mesoionic forms. Certain irregularities in the absorption of highly substituted thiazoles are attributed to steric interactions.

EARLIER studies (Wilson, *J.*, 1955, 1389) of the reaction of tetrahydro-2-thioglyoxaline with alkyl halides and alkylene dihalides have now been extended to its reaction with α-halogenated carbonyl compounds. The products (Table 3, p. 2945) are formulated as 4′ : 5′-dihydroglyoxalino(2′ : 1′-2 : 3)thiazolium salts (I) on the basis of their ultraviolet light absorption properties (discussed below) and by analogy with the formation of monocyclic thiazoles from thiourea and α-halogenated carbonyl compounds. The salts (I) contain the same skeleton as "4 : 5-dihydroglyoxalino-2-thioglycollo-1-lactam" (Stephen and F. J. Wilson, *J.*, 1926, 2532); several derivatives of the aromatic parent system (II) have also been described (Ochiai, *Ber.*, 1936, **69**, 1650; Andersag and Westphal, *ibid.*, 1937, **70**, 2035; Kondo and Nagasawa, *J. Pharm. Soc. Japan*, 1937, **57**, 1050; Matsukawa and Ban, *ibid.*, 1951, **71**, 756). Alkali converted the salts (I) into the bicyclic bases (III) (Table 3B); the structures of these bases and of other 2-iminothiazolines are discussed below.



There is little published information on the ultraviolet absorption of thiazoles. Ruehle (*J. Amer. Chem. Soc.*, 1935, **57**, 1887) studied a few simple thiazoles; however, the band at 225 mμ (ε 13,000) reported for 4-methylthiazole ethiodide is probably iodide ion absorption (cf. Head and Standing, *J.*, 1952, 1457). Thiazole itself has $\lambda_{max.}$ 240 mμ (ε 4000) (Braude, *Ann. Reports*, 1945, **42**, 128). The few 2-amino- and dihydro-2-imino-thiazoles which have been compared appear to have similar spectra (Vandenbelt and Doub, *J. Amer. Chem. Soc.*, 1944, **66**, 1633; Shepherd, Bratton, and Blanchard, *ibid.*, 1942, **64**, 2532). However, there appear to be differences between the absorption of 2-amino- and dihydro-2-imino-benzothiazoles (Edisbury, Hunter, and Scott, *J.*, 1948, 1497), and in view of the successful application of ultraviolet absorption studies to tautomeric 2-aminopyridine systems (Anderson and Seeger, *J. Amer. Chem. Soc.*, 1949, **71**, 340; Gol'dfarb, Setkina, and Danyushevskii, *J. Gen. Chem. U.S.S.R.*, 1948, **18**, 124) further work on 2-iminothiazolines was desirable. The ultraviolet absorption properties of several thiazoles, more complex

than those discussed here, have been reported (Cook, Heilbron, *et al.*, *J.*, 1947, 1598; 1948, 201, 2031; Stern, *J.*, 1949, 1664; Yamamoto, *J. Pharm. Soc. Japan*, 1951, **71**, 662).

The ultraviolet absorption characteristics of a number of thiazole derivatives, in each case as the base and as the salt, have been measured (Table 1). The introduction of a methyl group at position 4 or 5 or into a 2-amino-group of simple thiazoles has a small bathochromic effect (2—6 mμ), which is seen in both bases and salts. A 4-benzyl group has a similar effect. Methylation of more highly substituted thiazoles sometimes results in a hypsochromic shift, presumably because of steric interaction between the methyl and adjacent groups (see below). Classical tautomerism is impossible in the 2-diethylaminothiazole (18) and in the 2-iminothiazolines (31) and (25); these three compounds have comparable light absorption either as base or as salt. These results confirm the view

TABLE 1. *Ultraviolet light absorption, in ethanol, of thiazoles and 2-iminothiazolines.*

					Salt		Base	
No.	$R_{(2)}$	$R_{(3)}$	$R_{(4)}$	$R_{(5)}$	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
1	Dihydroglyoxalino		H	H	264	7,100	270	7,400
2	,,		Me	H	268	6,700	270	8,000
3	,,		Ph·CH_2	H	267	7,400	268	8,700
							234	23,300
4	,,		Ph	H	269	13,200	264	8,400
							310	4,700
5	,,		Ph	Me	272	10,600	234	27,000
							293	7,500
6	,,		Me	Ph	288	12,800	282	8,100
							325	9,800
7	,,		Ph·CH_2	Ph	286	12,600	280	7,300
							324	9,200
8	NH_2	—	Me	H	260	7,300	259	6,400
9	NH_2	—	Ph·CH_2	H	259	7,600	257	5,800
10	NH_2	—	Ph	H	265	16,650	228	23,000
							284	8,000
11	NH_2	—	Ph	Me	265	12,000	256	9,100
12	NH_2	—	H	Ph	290	16,200	308	16,500
13	NH_2	—	Me	Ph	280	13,100	293	11,200
14	NH_2	—	Ph·CH_2	Ph	278	13,200	295	11,500
15	NHMe	—	H	H	258	8,700	261	7,300
16	NHMe	—	Me	H	263	8,700	262	7,300
17	NHMe	—	Ph	H	269	17,500	232	21,400
							288	5,700
18	NEt_2	—	Me	H	224	2,900	269	8,400
					269	9,600		
19	NH_2	—	H	H	255	8,000	255	6,300
20	H	—	Ph	H	252	13,900	252	13,900
21	H	—	Ph	Me	244	11,100	249	11,700
22	H	—	H	Ph	275	12,800	275	12,800
23	H	—	Me	Ph	275	8,500	267	10,700
24	H	—	Me	H	248	3,600	244	3,300
25	:NMe	Me	H	H	255	7,100	259	6,300
26	:NMe	Me	Me	H	260	7,600	257	8,200
27	:NMe	Me	Ph	H	260	12,300	250	9,600
							300	3,900
28	:NMe	Me	Ph	Me	263	11,100	258	9,800
29	:NPh	Ph	Ph	Me	283	9,500	292	11,200
30	:NPh	Ph	Me	Ph	294	12,900	317	13,800
31	:NH	Me	H	H	254	6,800	260	6,400
32	:NH	Me	Me	H	259	6,500	264	6,900
33	:NH	Me	Ph	H	258	10,900	255	8,400
							300	3,900

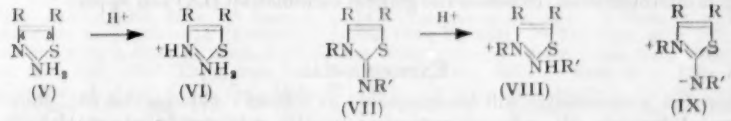
Notes: [8] Salt, $\lambda_{max.}$ 259 mμ (ε 5800) in 95% EtOH (Conover and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 5221). [23] Hydrochloride, $\lambda_{max.}$ 250 mμ (ε 4000), in H_2O (Ruehle, *loc. cit.*). [21] Base, $\lambda_{max.}$ 258 mμ (ε 8000) in EtOH (Shepherd, Bratton, and Blanchard, *loc. cit.*). [19] Base, $\lambda_{max.}$ 254 mμ (ε 6000); hydrochloride, $\lambda_{max.}$ 254 mμ (ε 8000) in H_2O (Vandenbelt and Doub, *loc. cit.*).

(Vandenbelt and Doub, *loc. cit.*) that ultraviolet absorption studies cannot diagnose the tautomeric state of 2-aminothiazoles. It has been established recently by infrared studies that 2-aminothiazole exists as such, and not as 2-iminothiazoline (Angyal and Werner, *J.*, 1952, 2911; cf. Angyal and Angyal, *J.*, 1952, 1461).

Dihydroglyoxalinothiazolium salts and 3-methyl-2-methylaminothiazolium salts are similar in structure; however, the bicyclic compounds absorb at 8—9 mμ longer wavelengths than equivalently substituted monocyclic ones; there is an even greater difference (11—13 mμ) between some of the bases in these two series. The dihydroglyoxaline ring thus has a marked bathochromic effect, which may be associated with ring strain; in that connection, bicyclic thiazoles (IV; $n = 3$) which also have an additional non-aromatic five-membered ring, absorb much less intensely than homologues (IV; $n = 4$) (Erlenmeyer and Schoenauer, *Helv. Chim. Acta*, 1941, **24**, 172E; Erlenmeyer and Bischoff, *ibid.*, 1946, **29**, 280). Steric distortion of chromophoric systems usually results in hypsochromic shifts and/or reduction in intensity (*e.g.*, Braude, Sondheimer, and Forbes, *Nature*, 1954, **173**, 117), although apparent bathochromic shifts have been observed in a few special cases (Meek, Turnbull, and Wilson, *J.*, 1953, 2894).

TABLE 2. *Dipole moments of bases in benzene.*

No.	8	16	10	17	32	26	2	4
Moment (D)	1·8	1·6	2·1	2·3	3·3	3·3	4·2	4·2



The superficial similarity between the absorption curves of 4- or 5-phenylthiazole and 4-methylthiazole is probably not significant; the much more intense absorption of the phenyl compounds is probably a "*K*" band, whilst the non-phenylated compounds exhibit "*B*" bands (cf. Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Arnold, London, 1954, p. 125). 2-Amino-5-phenylthiazole hydrochloride (12) absorbs at considerably longer wavelengths than the 4-phenyl

TABLE 3. 4′ : 5′-*Dihydroglyoxalino*(2′ : 1′-2 : 3)*thiazolium salts* (I).

No.	$R_{(4)}$	$R_{(5)}$	Halide used	Yield (%)	M. p.	Formula	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H
1	H	H	A	70	183—186°	Hygroscopic, not analysed				
2	Me	H	B	94	258—259	$C_6H_9N_2SCl$	40·95	5·15	40·8	5·15
3	Ph·CH_2	H	G	72	181—183	$C_{12}H_{13}N_2SBr$	48·95	4·35	48·5	4·4
4	Ph	H	C	40	243—244	$C_{11}H_{11}N_2SBr$	46·95	4·0	46·65	3·9
5	Ph	Me	D	80	236—239	$C_{12}H_{13}N_2SBr$	47·6	4·55	48·5	4·4
6	Me	Ph	F	61	246—248	$C_{12}H_{13}N_2SBr$	48·45	4·65	48·5	4·4
7	Ph·CH_2	Ph	H	90	193—194	$C_{14}H_{17}N_2SBr$	57·7	4·45	57·9	4·6

TABLE 3B. *Bicyclic bases* (III) *from dihydroglyoxalinothiazolium salts.*

From salt no.	M. p.	Formula	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H
1	84—86°	$C_5H_6N_2S$	47·9	4·8	47·6	4·8
2	90—92	$C_6H_8N_2S,\frac{1}{2}H_2O$	48·6	5·85	48·3	6·1
3	Oil	Unstable, not analysed				
4	111—113	$C_{11}H_{10}N_2S$	65·3	5·05	65·3	5·0
5	90·5—91·5	$C_{12}H_{12}N_2S$	66·4	5·65	66·6	5·6
6	121—124	$C_{12}H_{12}N_2S$	66·2	6·1	66·6	5·6
7	102—103	$C_{15}H_{16}N_2S$	74·5	5·55	73·95	5·5

isomer (10); a similar effect has been observed with the analogous 4- and 5-ethoxycarbonyl compounds (Conover and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 5221). The absorption curves of 2-amino-4-phenylthiazole bases are usually complex, having a main peak, together with a very broad, intense band, within which a second peak can be defined only approximately. 5-Methyl-4-phenylthiazole (21) has anomalous light absorption properties; the hydrochloride absorbs at lower wavelengths (2 mμ) and much less intensely than 4-phenylthiazole hydrochloride (19), and similar effects are seen when the bases are compared. These results are attributed to steric interaction between the methyl and the phenyl group, as

in *o*-substituted diphenyls (*e.g.*, Friedel and Orchin, "Ultra-violet Spectra of Aromatic Compounds," Wiley, New York, 1951). Other examples of this phenomenon can be drawn from Table 1, whilst Knott (*J.*, 1952, 4099) has adduced evidence for steric interaction between 4-phenyl groups and adjacent substituents in more complex thiazole derivatives.

It has been noted already that equivalently substituted 2-aminothiazoles (V) and 2-iminothiazolines (VII) have similar ultraviolet light absorption. This might be expected with the salts, for which the almost identical structures (VI) and (VIII) respectively can be written (cf. Conover and Tarbell, *loc. cit.*). The spectral similarity between the bases (V) and (VII) is surprising, and suggests that the iminothiazolines retain a more or less intact thiazole chromophore, as in the mesoionic forms (IX). In accordance with such structures, 2-iminothiazolines have been found to have a higher dipole moment (Table 2); the values found for 2-aminothiazoles are comparable with values of 1·64 D reported for thiazole and 1·75 D for 2-aminothiazole (Jensen and Friediger, *Kgl. Danske Videnskab. Selskab*, 1943, **20**, No. 2, 1; *Chem Abs.*, 1945, **39**, 2068). Mesoionic structures analogous to (IX) have been suggested in the benzothiazole series on similar evidence (Brooker, Keyes, Smyth, and Oesper, *J. Amer. Chem. Soc.*, 1941, **63**, 3192). The bicyclic bases (III) are also 2-iminothiazolines, to which the general formulation (IX) can apply.

Experimental

Halogenated intermediates will be designated as follows: chloroacetal (A), chloroacetone (B), phenacyl bromide (C), α-bromopropiophenone (D), α-bromophenylacetaldehyde diethyl acetal (E), 1-bromo-1-phenylpropan-2-one (F), 3-bromo-1-phenylpropan-2-one (G), 1-bromo-1-phenylpropan-2-one (H). Compounds (F), (G), and (H) were made by methods described by Smith and Wilson (*J.*, 1955, 1342). Bromination of acetophenone (Ward, *J.*, 1923, 2211) and of propiophenone (Pampel and Schmidt, *Ber.*, 1886, **19**, 2897; Kunckell and Dettmar, *Ber.*, 1903, **36**, 771) gave (C) (80%, m. p. 48°) and (D) (b. p. 125—130°/10 mm.) respectively; (E) (45%; b. p. 124—130°/8 mm.) was made by Bedoukian's method (*J. Amer. Chem. Soc.*, 1944, **66**, 1325). Chloroacetone diethyl ketal (b. p. 64—69°/28 mm.) was obtained in 86% yield (Ewlampiew, *Ber.*, 1929, **62**, 2387). Tetrahydro-2-thioglyoxaline (82%; m. p. 199—200°) was made by the method of *Org. Synth.*, 1946, **26**, 34. Methyl *iso*thiocyanate (*Org. Synth.*, 1941, **21**, 81) with aqueous ammonia or methylamine gave *N*-methylthiourea (65%; m. p. 117—118°) and *NN'*-dimethylthiourea (73%; 56—58°). A mixture of ethanol (50 c.c.), 2-dimethylaminoethanol (5 c.c.), and diethylcyanamide (20 g.) was heated at 45—50° for 14 hr., in a stream of hydrogen sulphide. On cooling, *NN*-diethylthiourea (18 g., 68%; m. p. 101—103°) separated (Wallach, *Ber.*, 1899, **32**, 1874, gives m. p. 101—102°).

4' : 5'-Dihydroglyoxalino(2' : 1'-2 : 3)thiazolium Salts (*Table* 3).—Molar quantities of tetrahydro-2-thioglyoxaline and α-halogenated carbonyl compounds were refluxed in ethanol for 2 hr. The colourless *products* which separated on evaporation and cooling were recrystallised from ethanol. Chloroacetone and chloroacetone diethyl ketal gave the same product. The acetal (A) reacted readily in the presence of a few drops of concentrated hydrochloric acid; (E) did not react, even in the presence of free hydrochloric acid. The colourless bases (Table 3B) usually separated when sodium hydroxide was added to aqueous solutions of the thiazolium salts. The bases were appreciably soluble in ether, and were purified by sublimation at 0·01 mm., or by recrystallisation from benzene–light petroleum (b. p. 40—60°). The two simplest bases were soluble in cold water.

Substituted 2-Aminothiazoles (*Table* 4).—Reaction of α-halogenated carbonyl compounds with thiourea gave compounds nos. (8)—(14) inclusive. Nos. (15), (16), and (17) were similarly obtained from *N*-methylthiourea, and (18) from *NN*-diethylthiourea. It was necessary to add a few drops of concentrated hydrochloric acid in reactions with chloroacetal. The simpler thiazolium salts were hygroscopic; the bases were obtained from the salts by addition of alkali and filtration or ether-extraction. 2-Aminothiazole (19) was a purified commercial sample.

Thiazoles (*Table* 4).—Compounds (21), (23), and (24) were made by warming α-halogenated carbonyl compounds with freshly prepared thioformamide, followed by neutralisation with ammonia and steam-distillation (cf. Erlenmeyer and Simon, *Helv. Chim. Acta*, 1942, **25**, 528). Compound (20) was made by Russel's method (U.S.P. 2,509,453), and (22) from ω-amino-acetophenone (Ohta, *J. Pharm. Soc. Japan*, 1951, **71**, 869).

TABLE 4. *Thiazoles.*

No.	Halide used	Salt	Yield (%)	M. p.	Base, m. p.
8	B	HCl	73	170—171°	38—39°
9	G	HBr	—	88—90	93—94
10	C	HBr	80	184—186	150—152
11	D	HBr	83	172—175	118—119
12	E	—	—	—	204—206 (20% yield)
13	F	HBr	55	214—216	164—166
14	H	HBr	70	215—216	143—144
15	A	HCl	Very hygroscopic		b. p. 106—107/16 mm.
16	B	HCl	65	226—227	66—69
17	C	HBr	—	149—151	136—137 (85% yield)
18	B	HCl	Syrup		b. p. 100—102/8 mm. (94% yield)
20	C	—	—	—	51—52
21	D	—	—	—	b. p. 140—142/12 mm.
22	—	—	—	—	44—45
23	F	—	—	—	b. p. 134—136/20 mm.
24	B	—	—	—	b. p. 131—132

Notes: [8] Base, m. p. 42° (Traumann, *Annalen*, 1888, **249**, 37); m. p. 44—45° (*Org. Synth.*, Coll. Vol. II, p. 31); m. p. 42°, hydrochloride, m. p. 169—171° (Lanfranchi, *Atti R. Accad. Lincei*, 1942, **3**, 776). [9] The base, m. p. 96—97°, has been made by a different method (Libermann and Moyeux, *Bull. Soc. chim. France*, 1950, 301). [10] Base, m. p. 147° (Traumann, *loc. cit.*). [11] Base, m. p. 124—125°, hydrobromide, m. p. 170—173° (Szekeres, *Gazzetta*, 1948, **78**, 681). [12] The base, m. p. 207·5—208·5°, has been made by a different method (Hurd and Wehrmeister, *J. Amer. Chem. Soc.*, 1949, **71**, 4007). [13] Base, m. p. 164—166° (Kopp, *Bull. Soc. chim. France*, 1950, 582). [14] Base, m. p. 139—140° (King and Hlavacek, *J. Amer. Chem. Soc.*, 1950, **72**, 3722). [15] Hydrochloride, m. p. 79—80°, hygroscopic (Näf, *Annalen*, 1891, **265**, 113). [16] Base, m. p. 71·5—72·5°; hydrochloride, m. p. 228° (Burtles, Pyman, and Roylance, *J.*, 1925, 588). [17] Base, m. p. 138° (Traumann, *loc. cit.*, p. 46). [18] Base, b. p. 103°/10 mm. (Ochiai and Kashida, *J. Pharm. Soc. Japan*, 1942, **62**, 97). [20] Base, prepared by another method, m. p. 52° (Popp, *Annalen*, 1889, **250**, 279); 55° (Russel, *loc. cit.*). [21] Base, b. p. 110—111°/2 mm. (Ochiai, Kakuda, Nakayama, and Masuda, *J. Pharm. Soc. Japan*, 1939, **59**, 462; b. p. 278° (Merck, G.P. 670,131). [22] Base, m. p. 45—46° (Ohta, *J. Pharm. Soc. Japan*, 1951, **71**, 869). [23] Base, b. p. 134—135°/25 mm. (Erlenmeyer and Simon, *Helv. Chim. Acta*, 1942, **25**, 528). [24] Base, b. p. 131° (Merck, *loc. cit.*; cf. Ganapathi and Venkataraman, *Proc. Indian Acad. Sci.*, 1946, **22**, *A*, 343).

TABLE 5. *2-Iminothiazolines.*

No.	Halide used	Salt	Yield (%)	M. p.	Base, m. p.
25	A	HCl	72	235—236°	Oil
26	B	HCl	84	198—199	96—97
27	C	HBr	77	197—198	76—77
28	D	HBr	82	242—244 (dec.)	62—63
29	D	—	—	—	179 (58% yield)
30	F	HBr	60	270—272	170—173
31	—	HI	85	184—185	b. p. 104—109°/16 mm., m. p. 36—37°
32	—	HI	83	167—168	b. p. 122—123°/16 mm.
33	—	HI	85	231—233 (dec.)	Syrup

Notes: [25] Hydrochloride, m. p. 222° (Näf, *Annalen*, 1891, **265**, 116). [26] Base, m. p. 96° (Traumann, *Annalen*, 1888, **249**, 49). [27] *Base* (Found: C, 64·8; H, 6·0. $C_{11}H_{12}N_2S$ requires C, 64·7; H, 5·9%). [28] *Base* (Found: C, 65·7; H, 6·4. $C_{12}H_{14}N_2S$ requires C, 66·0; H, 6·45%); *hydrobromide* (Found: C, 47·85; H, 4·95. $C_{12}H_{14}N_2S$,HBr requires C, 48·15; H, 5·05%). [29] *Base* (Found: C, 76·95; H, 5·35. $C_{22}H_{18}N_2S$ requires C, 77·15; H, 5·3%). [30] *Hydrobromide* (Found: C, 62·75; H, 4·75. $C_{22}H_{18}N_2S$,HBr requires C, 62·4; H, 4·5%); *base* (Found: C, 77·4; H, 5·15. $C_{22}H_{18}N_2S$ requires C, 77·15; H, 5·3%). [31] Hydriodide, m. p. 175° (Näf, *loc. cit.*); m. p. 182—184°; base, b. p. 96—98°/11 mm., m. p. 44—45° (Druey, *Helv. Chim. Acta*, 1941, **24**, 226E). [32] Base, m. p. 47·5° (Traumann, *loc. cit.*, p. 44). [33] Base is an oil (Traumann, *loc. cit.*).

2-Iminothiazolines (*Table 5*).—Appropriate 2-aminothiazoles were refluxed for 2 hr. with methyl iodide in ethanol or propanol, to give the 2-imino-3-methylthiazoline hydriodides (31), (32), and (33). 2-Imino-3 : 4-dimethylthiazoline was obtained from the salt by addition of alcoholic potassium hydroxide and ether-extraction. Reaction of α-halogenated carbonyl compounds with *NN′*-diphenylthiourea gave compounds (29) and (30); compounds (25), (26), (27), and (28) were obtained similarly from *NN′*-dimethylthiourea. Compound (29) was weakly basic and separated from the reaction mixture as the base. The hydrobromide (30) was insoluble in water, and the base was obtained by passing dry ammonia through a chloroform solution of the salt, filtering off the ammonium bromide, and evaporating the solvent.

Physical Measurements.—Light absorption measurements (Table 1) were made with a Unicam SP. 500 spectrophotometer, with 10-mm. cells. "P.I. Rectified Spirit," which gives ⩾50% transmission of light down to 205 mμ and is cheap, was used as solvent. The absorption

of salts was measured on solutions made from either the salts or the bases, 2 drops of concentrated hydrochloric acid being added to the absorption cells. Solutions of the bases were made directly, or by adding 2 drops of 10% sodium hydroxide to cells containing solutions of the salts.

The dipole moments (Table 2) were measured by using the simple apparatus described by Bender (*J. Chem. Educ.*, **1946**, **23**, 179), and are accurate to $\pm 0{\cdot}2$ D. Concentrations of about 4 g./l. in dry benzene were employed. Compound (2) (base) gave the following dipole moments at different concentrations: 0·0106 (mole fraction), 4·23 D; 0·0077, 4·21 D; 0·0032, 4·33 D; 0·00095, 4·36 D. Evidently, there is negligible association in benzene (contrast glyoxalines, Jensen and Friediger, *loc. cit.*).

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The Chemistry of Extractives from Hardwoods. Part XXV. (−)-epiAfzelechin, a New Member of the Catechin Series.*

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Ether-extracts of the heartwood of *Afzelia* species contain kaempferol, dihydrokaempferol, and a previously unknown 3 : 5 : 7 : 4′-tetrahydroxyflavan. The new flavan closely resembles the 3 : 5 : 7 : 3′ : 4′-pentahydroxy-compound *epi*catechin and has thus been named *epi*afzelechin. The configurations of catechin and of *epi*catechin, concerning which there has hitherto been some ambiguity, have been re-examined in the light of current stereochemical theory, whereby the *cis*-conformation has been established for *epi*catechin and hence for its analogue *epi*afzelechin.

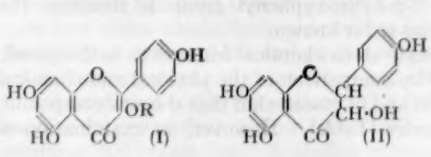
The investigation of a powdery material occluded in a sample of the commercial timber derived from *Afzelia* species revealed the occurrence of a kaempferol 3-rhamnoside, afzelin (I; R = $C_6H_{11}O_4$) (King and Acheson, *J.*, 1950, 168). The glycoside was accompanied by a small amount of a colourless compound $C_{15}H_{12}O_6$ provisionally described as a dihydrotetrahydroxyflavone, which at the time of its isolation had not been listed in abstract indexes. This substance has since been identified as a partly racemised specimen of (+)-dihydrokaempferol (II), previously found in the Japanese Judas tree (*Cercidiphyllum japonicum*) and named katuranin by Uoda, Fukushima, and Kondo (*J. Agric. Chem. Soc. Japan*, **1943**, **19**, 467). We thank Professor S. Hattori for drawing attention in 1950 (personal communication) to the resemblance of the compound $C_{15}H_{12}O_6$ to katuranin, and for a specimen of the latter obtained from *C. japonicum* by Dr. M. Hasegawa (see *Chem. Abstr.*, **1953**, **47**, 858) by which we have been able to confirm the identity of the product from afzelia wood. (+)-Dihydrokaempferol has also been found in *Nothofagus dombeyi* by Pew (*J. Amer. Chem. Soc.*, **1948**, **70**, 3031) and with dihydroquercetin in the heartwood of *Larix decidua* by Gripenberg (*Acta Chem. Scand.*, 1952, **6**, 1152). The compound aromadendrin, long known as a constituent of *Eucalyptus kino*, has also been recognised as (+)-dihydrokaempferol (Hillis, *Austral. J. Sci. Res.*, 1952, **5**, 379).

The extractives of the heartwood of *Afzelia* species have now been examined; specimens from various commercial sources were used and their derivation from members of the genus *Afzelia* was confirmed by Mr. B. J. Rendle, D.S.I.R. Forest Products Laboratory. Anatomical examination of the wood specimens alone is insufficient, however, to differentiate the individual species, and the precise botanical origin of the material could not therefore be ascertained.

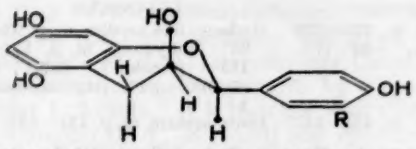
* Part XXIV, *J.*, 1955, 1338.

A colourless waxy material was first removed from the shredded wood with boiling light petroleum. Further extraction with boiling ether gave kaempferol (I; R = H), impure (+)-dihydrokaempferol (II), and a lævorotatory compound $C_{15}H_{14}O_5$, which with acids showed a marked inclination to polymerise. From its resemblance to the catechins (III; R = H), and in particular to *epi*catechin, this new product was later termed (−)-*epi*afzelechin and was ultimately identified as (IV). The three compounds were separated by treatment with hot water in which kaempferol is virtually insoluble; dihydrokaempferol—sometimes appreciably racemised—crystallises from the aqueous filtrate, and *epi*afzelechin is found in the residual solution. The rhamnoside afzelin (I; R = $C_6H_{11}O_4$) has not so far been encountered as a normal heartwood constituent, although it was again present among the contents (amounting to 25 g.) of a fissure in a further sample of the wood, the water-soluble glycoside being apparently the form in which the phenolic and presumably fungicidal component kaempferol is readily transported to the damaged tissues. As with the heartwood extractive, small amounts of dihydrokaempferol and of *epi*afzelechin were also found in the shake (fissure) contents, but in neither material was detected any compound of the intermediate flavan-3 : 4-diol series similar to the *leuco*anthocyanidin melacacidin (King and Bottomley, *J.*, 1954, 1399).

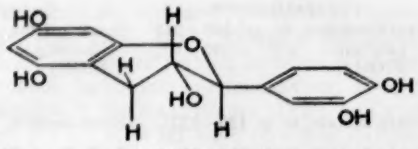
*epi*Afzelechin yields a tetra-acetate and thus contains four hydroxyl groups of which three were shown to be phenolic by the formation of an alkali-insoluble trimethyl ether affording a monoacetate and toluene-*p*-sulphonate. The latter ester develops an orange colour on exposure to the atmosphere, a property later ascribed to the formation of 5 : 7 : 4′-trimethoxyflavylium toluene-*p*-sulphonate. The new flavan-3-ol possesses the typical catechin reactions (see experimental section), and the positive vanillin–hydrochloric acid test indicated the presence of a phloroglucinol nucleus.



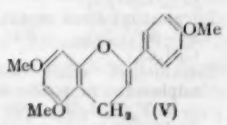
(I) (II) (III) (IV)



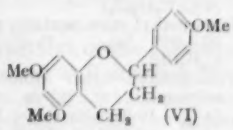
(IV*A*) *epi*Catechin (R = OH). *epi*Afzelechin (R = H)



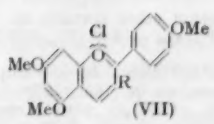
(IV*B*) Catechin



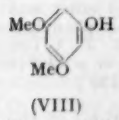
(V)



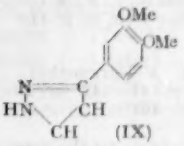
(VI)



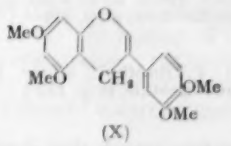
(VII)



(VIII)



(IX)



(X)

Oxidation of the trimethyl ether with potassium permanganate in acetone produced *p*-anisic acid and in conjunction with the data already outlined this led to the tentative adoption of structure (IV).

When the 5 : 7 : 4′-trimethyl ether 3-toluene-*p*-sulphonate was treated with anhydrous hydrazine it was smoothly converted into the flaven (V), thus resembling the corresponding

*epi*catechin derivative (Freudenberg, Fikentscher, and Harder, *Annalen*, 1925, **441**, 157) and in contrast to the analogous catechin ester which undergoes disintegration (*vide infra* and Freudenberg, Orthner, and Fikentscher, *Annalen*, 1924, **436**, 286). The flaven (V) exhibited the expected light absorption and was catalytically reduced by one molecular equivalent of hydrogen to the flavan (VI) indistinguishable from (±)-5 : 7 : 4′-trimethoxyflavan prepared by a similar reduction of 5 : 7 : 4′-trimethylapigenidin chloride (VII; R = H). Conversely, the flaven (V) was converted into the flavylium chloride (VII; R = H) by atmospheric oxidation in presence of hydrogen chloride (cf. similar oxidations, Baker, *J.*, 1929, 1593).

Corroborative evidence for the structure (IV) was obtained by catalytic hydrogenation of 5 : 7 : 4′-trimethylpelargonidin chloride (VII; R = OH) to (±)-*epi*afzelechin trimethyl ether, m. p. 105°, the latter having an ultraviolet absorption identical with that of the natural compound, m. p. 110° (mixed m. p. 105°). Similarly, natural trimethyl*epi*afzelechin acetate, m. p. 133°, did not depress the m. p. of the corresponding racemic acetate, m. p. 123°. Finally, comparison of the infrared absorption of the two methyl ethers and of their acetates in carbon tetrachloride solution was carried out by Dr. F. B. Strauss (through the kindness of Sir Robert Robinson, O.M., F.R.S.) who reports that, despite certain restrictions due to the solvent, sufficient absorption bands are present in the spectra to establish the relationship of the respective derivatives. Thus afzelechin is related to the flavonol kaempferol as the catechins are to quercetin. The gallocatechins (III; R = OH), an analogous group based on the flavonol myricetin, contain a pyrogallol residue as 2-substituent. These comprise a racemate (Bradfield and Penney, *J.*, 1948, 2249), a dextrorotatory isomer casuarin (Oshima, *J. Agric. Chem. Soc. Japan*, 1939, **15**, 636), and the gallocatechin isolated from tea by Tsujimura (*Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1925, **10**, 252). The new catechin with its 2-*p*-hydroxyphenyl group is therefore the simplest naturally occurring example of the series so far known.

The derivation of formula (IV) now leaves only stereochemical features to be discussed, although the fact has already been established by comparison of the physical and chemical properties of *epi*afzelechin with those of catechin and of *epi*catechin that the new compound, as its name implies, is a member of the *epi*-series (Table). However, an examination of

(−)-*epi*Afzelechin	(−)-*epi*Catechin	(+)-Catechin
Small needles, m. p. 240—243° (decomp.), $[\alpha]_D^{19}$ −59° (5%, EtOH)	Stout prisms, m. p. 237—239° (decomp.), $[\alpha]_{Hg}$ −69° (7%, EtOH)	Hydrate, fine needles, m. p. 93—95°; anhydrous, m. p. 174—175° (decomp.), $[\alpha]_{Hg}^{0}$ 0° (EtOH), +17° (H_2O–acetone; 1 : 1)
Tetra-acetate, m. p. 126—127°	Penta-acetate, m. p. 151—152°	Penta-acetate, m. p. 131—132°
5 : 7 : 4′-Trimethyl ether, m. p. 110°, $[\alpha]_D^{19}$ −67° (2%, EtOH)	5 : 7 : 3′ : 4′-Tetramethyl ether, m. p. 153—154°, $[\alpha]_{Hg}$ −61·5° (4%, $C_2H_2Cl_4$)	5 : 7 : 3′ : 4′-Tetramethyl ether, m. p. 143—144°, $[\alpha]_{Hg}$ −13·4° (3%, $C_2H_2Cl_4$)
Trimethyl ether acetate, m. p. 133°, $[\alpha]_D$ −73·8° (2%, $CHCl_3$)	Tetramethyl ether acetate, m. p. 91—92°, $[\alpha]_{Hg}$ −71·2° (5%, $C_2H_2Cl_4$)	Tetramethyl ether acetate, m. p. 95—96°, $[\alpha]_{Hg}$ +6·8° (10%, $C_2H_2Cl_4$)
Trimethyl ether toluene-*p*-sulphonate, m. p. 165°, $[\alpha]_D^{19}$ −9° (3%, $CHCl_3$), with anhyd. hydrazine yields 5 : 7 : 4′-trimethoxyflav-2-en, m. p. 129—130°	Tetramethyl ether toluene-*p*-sulphonate, m. p. *ca.* 165°, $[\alpha]_{Hg}^{17}$ −16·9°, with anhyd. hydrazine yields 5 : 7 : 3′ : 4′-tetramethoxyflav-2-en, m. p. 119°	Tetramethyl ether toluene-*p*-sulphonate, m. p. 86—87°, $[\alpha]_D^{14}$ +22·7° ($C_2H_2Cl_4$), with anhyd. hydrazine yields mainly fission products (phloroglucinol dimethyl ether and 3-3′ : 4′-dimethoxyphenylpyrazoline)
(±)-5 : 7 : 4′-Trimethyl ether, m. p. 105° (acetate, m. p. 123°)	(±)-5 : 7 : 3′ : 4′-Tetramethyl ether, m. p. 141—142° (acetate, m. p. 160—161°)	(±)-5 : 7 : 3′ : 4′-Tetramethyl ether, m. p. 142° (acetate, m. p. 134—135°)

the literature reveals that doubt still exists as to the true configurations of the diastereoisomeric catechins. Freudenberg in his earlier memoirs (*Annalen*, 1925, **441**, 157; **443**, 309; **446**, 87) supposed catechin to have the *cis*-structure ($H_{(2)}$ and $H_{(3)}$ *cis*) and that in the isomeric *epi*catechin the configuration was *trans*, but later this assertion was withdrawn and the question was left undecided (*Annalen*, 1927, **451**, 214; *J. Amer. Chem. Soc.*, 1932, **54**, 1917). Others, *e.g.*, Geissman and Lischner (*J. Amer. Chem. Soc.*, 1952, **74**, 3001) and

Hergert and Kurth (*J. Org. Chem.*, 1953, **18**, 521), later adopted the *cis*-structure for *epi*-catechin, the evidence on which this configuration had originally been attributed to catechin having been described by Hückel, Gerke, and Frank (*Annalen*, 1929, **477**, 159) as equivocal. On the other hand, Warburton in a recent review of *iso*flavones (*Quart. Rev.*, 1954, **8**, 67) represents catechin as the *cis*-isomer, which is in agreement with the convention adopted in " A Dictionary of Applied Chemistry " (Thorpe, 4th Ed., Vol. II, p. 43). In view of these conflicting conclusions we have re-examined the evidence concerning the stereochemistry of the catechins.

Molecular models of the conventional kind show that the heterocyclic nucleus present in the flavans is puckered and, if the concepts of the conformational theory of cyclic structures are applied to this group of compounds, the isomeric catechins can be represented by formulæ of the type (IV*A*; R = OH) and (IV*B*). With the aid of these conformational diagrams chemical differences between the two diastereoisomerides can readily be interpreted and it has thus been possible to deduce with certainty their respective stereochemical configurations. The action of hydrazine on the tetramethyl ether 3-toluene-*p*-sulphonates, for example, which as already stated affords a high yield of the related Δ^2-flaven from the *epi*catechin derivative, occurs less readily with the corresponding catechin ester and the main products are *OO*-dimethylphloroglucinol (VIII) and the pyrazoline (IX) (Freudenberg, Fikentscher, and Harder, *Annalen*, 1925, **441**, 157; Freudenberg, Orthner, and Fikentscher, *ibid.*, 1924, **436**, 286). Formation of the flaven (V) is attributed to the stereospecific *trans*-elimination (E_2) of toluene-*p*-sulphonic acid from the *epi*catechin ester, in which the four participating centres (indicated by black dots in IV*A*; R = OH) are co-planar. The configuration of groups in the catechin ester (cf. IV*B*) is unfavourable for the formation of (V), and it has been suggested that the observed products (VIII) and (IX) arise *via* the intermediate flav-3-en (Freudenberg, Carrara, and Cohn, *Annalen*, 1925, **446**, 87). The view that these eliminations proceed by an E_2 mechanism rather than E_1 is supported by the fact that fission of the carbon skeleton leading to (VIII) and (IX) occurs without molecular rearrangement, whereas when tetramethylcatechin toluene-*p*-sulphonate is heated with quinoline it yields the *iso*flaven (X) (Freudenberg, Carrara, and Cohn, *loc. cit.*). This may be interpreted as a slow heterolysis of the $C_{(3)}$–O bond and rearrangement of the resulting carbonium ion. A similar rearrangement occurs in the formation of 2-chloro-5 : 7 : 3′ : 4′-tetramethoxy*iso*flavan from tetramethylcatechin and phosphorus pentachloride (Drumm, MacMahon, and Ryan, *Proc. Roy. Irish Acad.*, 1923—24, **36**, *B*, 41; 149; 1929, **39**, *B*, 114; Freudenberg, Carrara, and Cohn, *loc. cit.*) which, in terms of current stereochemical theory, proceeds by a synchronous carbonium-ion mechanism, as with other 1 : 2-shifts. It is therefore clear that catechin is the *trans*-isomer (IV*B*), and that *epi*catechin (IV*A*; R = OH) and *epi*afzelechin (IV*A*; R = H) have *cis*-configurations. Further corroboration is to be found in the formation of the *epi*-series of compounds by catalytic reduction of anthocyanidin derivatives, a consequence of the expected *cis*-addition of hydrogen to the planar flavylium nucleus.

The probable stereochemical structures of the gallocatechins also may now be inferred from recorded data, the isomer obtained by Tsujimura (*loc. cit.*) belonging evidently to the *epi*-series from its close analogy in m. p. (218°) and specific rotation (−67·5°) to *epi*catechin (m. p. 237—239°; $[\alpha]_D$ −69°) and to *epi*afzelechin (m. p. 240—243°; $[\alpha]_D$ −59°). Similarly it can be argued that casuarin (m. p. 181—183°; $[\alpha]_D$ +19·7°) is the (+)-gallocatechin from its resemblance to (+)-catechin (m. p. 174—175°; $[\alpha]_D$ +17°). The isomers of catechin occur predominantly in the forms (+)-catechin and (−)-*epi*catechin; the isolation of (−)-*epi*afzelechin, and the existence of the gallocatechins as (−)-*epi*gallocatechin and (+)-gallocatechin, indicate an interesting uniformity in the naturally occurring geometrical species of this group of flavans.

Experimental

Except where otherwise indicated, alcoholic solutions were used for ultraviolet absorption measurements.

Isolation of Kaempferol (I; R = H) *and* (+)-*Dihydrokaempferol* (II).—Afzelia heartwood (2400 g.) was extracted in a Soxhlet apparatus with boiling light petroleum (b. p. 60—80°) for

12 hr. and then with ether for 16 hr.; evaporation of the ether left a residue (88 g., 3·7%). Repeated extraction of this residue with boiling water left an insoluble fraction of crude flavonol (*ca.* 10 g., 0·4%) which, by repeated crystallisation from acetic acid and from aqueous ethanol (50%), afforded kaempferol in small yellow prisms, m. p. 279—280° (decomp.) alone and when mixed with an authentic specimen (Found, in material dried at 110° *in vacuo*: C, 63·4; H, 3·5. Calc. for $C_{15}H_{10}O_6$: C, 62·9; H, 3·5%). Light absorption: $\lambda_{max.}$ 266 (ε 22,000) and 366 mμ (ε 17,000). Kaempferol tetra-acetate crystallised from water in colourless needles, m. p. 183°; Kostanecki, Lampe, and Tambor (*Ber.*, 1904, **37**, 2096) give m. p. 181°. Kaempferol tetramethyl ether crystallised from methanol in needles, m. p. 161—162° (Found: C, 66·7; H, 5·6; OMe, 35·1. Calc. for $C_{19}H_{18}O_6$: C, 66·7; H, 5·3; OMe, 36·3%). Ramchandra, Rao, and Seshadri record m. p. 165—166° (*Proc. Indian Acad. Sci.*, 1946, **24**, *A*, 456).

Dihydrokaempferol (II).—Crystallisation of the combined hot water extracts of the ether residue, after filtration from undissolved kaempferol, afforded partially racemised dihydrokaempferol dihydrate (20 g., 0·8%) in fine needles, m. p. 222—224° (Found: C, 56·1; H, 5·3. Calc. for $C_{15}H_{12}O_6,2H_2O$: C, 55·6; H, 5·0. Found, in material dried at 110° *in vacuo*: C, 62·8; H, 4·5; loss, 11·6. Calc. for $C_{15}H_{12}O_6$: C, 62·5; H, 4·2; loss, 11·1%), $[\alpha]_D$ +2·5° (1% in EtOH), $[\alpha]_D$ +9° (0·9% in acetone–H_2O, 1 : 1); literature values: $[\alpha]_D^{20}$ +46° (4% in acetone–H_2O, 1 : 1), $[\alpha]_D^{20}$ +13° (4% in EtOH) (Pew, *J. Amer. Chem. Soc.*, 1948, **70**, 3031). Light absorption: $\lambda_{max.}$ 214 (ε 28,000) and 292 mμ (ε 17,800). Dihydrokaempferol dihydrate became yellow when heated above 200° in soda-glass capillaries and melted at 222—224° (decomp.) after shrinking at 218°; in Pyrex capillaries, it had m. p. 246° (decomp., rapid rate of heating). The dependence of the m. p. on the type of glass capillary has been noted by Hillis (*Austral. J. Sci. Res.*, 1952, **5**, 379). Dihydrokaempferol from *Afzelia* heartwood proved indistinguishable from the compound $C_{15}H_{12}O_6,2H_2O$ obtained by King and Acheson (*J.*, 1950, 168) and also from katuranin, m. p. 224—225° (Uoda, Fukushima, and Kondo, *J. Agric. Chem. Soc. Japan*, 1943, **19**, 467—477), when the three specimens were examined by mixed m. p.s, paper chromatography (see below), and by colour reactions. Dihydrokaempferol gives a brownish-purple colour with aqueous ferric chloride and a pink coloration in the magnesium– and zinc–hydrochloric acid reactions.

Kaempferol tetra-acetate (1 g.), needles, m. p. and mixed m. p. 183—184°, was obtained by addition of acetic anhydride (5 g.) to dihydrokaempferol (3·6 g.) dissolved in a slight excess of aqueous sodium hydroxide (10%) at 0° (Found, in material dried at 110° *in vacuo*: C, 60·6; H, 4·5. Calc. for $C_{23}H_{18}O_{10}$: C, 60·8; H, 4·0%).

Isolation of (−)-epi*Afzelechin* (IV).—A sample of afzelia (2800 g.), of a somewhat lighter colour than that which had yielded kaempferol and dihydrokaempferol, was extracted with light petroleum (b. p. 60—80°; 24 hr.) and then with ether (24 hr.). The residue (*ca.* 20 g., 0·7%) obtained by evaporation of the ether-extract dissolved almost completely in hot water (1·5 l.), and insoluble material was discarded. After concentration under reduced pressure the aqueous solution (200 c.c.; charcoal) deposited a yellowish solid, m. p. 243—246° (decomp.) (15 g., 0·55%). Recrystallisation of this solid from aqueous ethanol (charcoal) afforded (−)-epi*afzelechin* [(−)-cis-3 : 5 : 7 : 4′-*tetrahydroxyflavan*] in colourless needles (9·1 g.), m. p. 240—243° (decomp.), $[\alpha]_D^{19}$ −58·9° (3% in EtOH) [Found: C, 65·5; H, 5·6%; *M* (Rast), 269. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·2%; *M*, 274]. Light absorption: $\lambda_{max.}$ 207 (ε 43,600) and 276 mμ (ε 2200). Concentration of the mother-liquors after collection of the tannin (9·1 g.) yielded a further 3·9 g., m. p. 239° (decomp.), and 1·2 g., m. p. 241° (decomp.), which shows that the original 15 g. consisted almost entirely of (−)-*epi*afzelechin. Isolation of the new tannin was greatly facilitated by the comparative freedom of this sample of wood from kaempferol and dihydrokaempferol. Subsequent extraction of other samples gave kaempferol (0·15—0·3%) and mixtures (0·15—0·6%) shown by paper chromatography to consist of dihydrokaempferol and (−)-*epi*afzelechin; a convenient separation of such mixtures has not yet been achieved.

Colour Reactions of (−)-epi*Afzelechin.*—(−)-*epi*Afzelechin gave no colour in the magnesium– or zinc–hydrochloric acid test, or when treated with sodium amalgam and subsequently acidified. A solution of vanillin in concentrated hydrochloric acid gave an immediate red colour with (−)-*epi*afzelechin. A methanolic solution gave a faint green colour with aqueous ferric chloride, but no colour was visible on paper chromatograms sprayed with the reagent. When warmed with concentrated sulphuric acid (−)-*epi*afzelechin gave an intense red colour which became more intense as gentle heating was continued, until finally obscured by charring; (+)-catechin behaved similarly in this respect. The red colour with sulphuric acid developed slowly in the cold, but rapidly in the presence of acetic anhydride. The catechin nature of (−)-*epi*afzelechin was revealed by the phlobaphene reaction: a solution of the tannin quickly formed a reddish

precipitate (phlobaphene) when boiled with concentrated hydrochloric acid; when *epi*afzelechin was boiled with dilute hydrochloric acid a yellowish-white precipitate was formed more slowly; with boiling dilute aqueous sodium hydroxide the tannin gave a yellow solution which yielded a pink precipitate after acidification. (−)-*epi*Afzelechin gave a dense white precipitate when boiled with aqueous formaldehyde; a similar precipitate developed more slowly by the acid-catalysed reaction in the cold.

3 : 5 : 7 : 4′-*Tetra-aceloxyflavan*.—A mixture of (−)-*epi*afzelechin (0·5 g.), sodium acetate (0·5 g.), and acetic anhydride (5 c.c.) was boiled for 2 hr. The residue obtained by evaporation of the solution was insoluble in water but freely soluble in aqueous methanol; the *tetra-acetate* crystallised from aqueous acetic acid in prisms, m. p. 121—122° raised to m. p. 126—127° by recrystallisation (Found: C, 62·0; H, 4·9; Ac, 39·5. $C_{23}H_{22}O_9$ requires C, 62·4; H, 5·0; Ac, 38·9%). The acetate gave an immediate red colour with cold sulphuric acid.

(−)-cis-**5 : 7 : 4′-*Trimethoxyflavan*-3-*ol*.**—A mixture of (−)-*epi*afzelechin (3·3 g.), anhydrous potassium carbonate (5·5 g., 3·3 mol.), methyl sulphate (1·7 c.c., 1·5 mol.), and dry acetone (50 c.c.) was boiled gently for 3 hr. before the addition of further methyl sulphate (1·7 c.c.), and gentle boiling was maintained until the following day; then aqueous ammonia and ether were added to the suspension. Concentration of the ethereal extracts, after washing with N-sodium hydroxide and water, afforded a residue (2·9 g., 76%) of crude (−)-cis-**5 : 7 : 4′-*trimethoxyflavan*-3-*ol***, m. p. **105—106°** raised by recrystallisation from methanol to m. p. 110° (prisms), $[\alpha]_D^{20}$ **−67·4°** (2% in EtOH) [Found: C, 68·5; H, 6·6; OMe, 28·3. $C_{18}H_{20}O_6$ requires C, 68·3; H, 6·4; OMe, 29·4%; *M*, by cryoscopic method in camphor (discoloration), 298, in exaltone, 332. Required: *M*, 316]: Light absorption: $\lambda_{max.}$ 208 (ε 53,400) and 274 mμ (ε 2190). The *acetate*, prepared by boiling the trimethyl ether with acetic anhydride, crystallised readily from ethanol in needles, m. p. **133°**, $[\alpha]_D^{21}$ **−73·8°** (2% in $CHCl_3$) (Found: C, 66·8; H, 6·25. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%). In carbon tetrachloride solution the carbonyl absorption band occurred at 5·75 μ.

The trimethyl ether and its acetate when warmed gently with concentrated sulphuric acid gave a red colour similar to that of (−)-*epi*afzelechin.

Potassium permanganate oxidation. A solution of (−)-*epi*afzelechin trimethyl ether (0·1512 g.) in acetone (50 c.c.) was heated on a boiling-water bath and treated with powdered potassium permanganate (1·8 g.) in portions until a faint pink colour persisted. A suspension in dilute sulphuric acid (20 c.c.) of the solid, collected by filtration, was treated with sulphur dioxide, and the resultant solution was boiled and filtered. *p*-Anisic acid (0·0153 g., 21%) crystallised from the cold solution in needles, m. p. and mixed m. p. 183—184°.

(−)-cis-**5 : 7 : 4′-*Trimethoxyflavan*-3-*ol Toluene*-p-*sulphonate*.**—An anhydrous pyridine (3 c.c.) solution of (−)-*epi*afzelechin trimethyl ether (1·5 g.) and toluene-*p*-sulphonyl chloride (1·2 g.) was heated on a steam-bath for 40 min. and then diluted with ethanol. The precipitated solid (1·1 g.), m. p. 162—163° (decomp.), was collected and washed with ethanol and with ether; the filtrate and washings yielded a further 0·3 g., m. p. 155° (total 1·4 g., 65%). The *toluene*-p-*sulphonate* crystallised from ethanol in needles, m. p. 165° (to an orange melt), $[\alpha]_D^{20}$ **−8·7°** (3% in $CHCl_3$) (Found, in material dried at 100° for ½ hr.: C, 63·4; H, 5·6. $C_{15}H_{24}O_7S$ requires C, 63·8; H, 5·6%). The formation and properties of this compound correspond closely with those of the (−)-*epi*catechin analogue (Freudenberg, Fikentscher, and Harder, *Annalen*, 1925, **441**, 157—180) including the fact that the yield is seriously diminished by extending the reaction time.

When exposed to air and light the toluene-*p*-sulphonate developed an orange colour on the surface resembling the colour of apigenidin trimethyl ether (which had $\lambda_{max.}$ 476 μ and $E_{1\,cm.}^{1\%}$ 1240 in 0·001N-hydrogen chloride in 95% ethanol). The nature of the colouring matter was confirmed by examination of a solution of the ester (0·08144 g./100 c.c. of 0·001N-HCl in ethanol) in the visible region, which revealed a single peak ($\lambda_{max.}$ 476 mμ, $E_{1\,cm.}^{1\%}$ 1·19) of the same shape and at the same position as that of the anthocyanidin; this observation is compatible with the presence in the ester examined of the equivalent of *ca.* 0·1% of apigenidin trimethyl ether. The orange coloration in the melt of the *epi*catechin analogue (Freudenberg *et al.*, *loc. cit.*) is doubtless caused by the formation of traces of luteolidin tetramethyl ether.

5 : 7 : 4′-*Trimethoxyflav*-2-*en* (V).—The foregoing ester (0·5154 g.) was heated with anhydrous hydrazine (20 c.c.) in a sealed tube at 132° (chlorobenzene vapour) for 40 min. Next day the needle crystals of **5 : 7 : 4′-*trimethoxyflav*-2-*en*** (0·1812 g., 55%), m. p. **129—130°** unchanged by recrystallisation from ethanol (needles), were collected on a sintered-glass Gooch crucible (Found: C, 72·4; H, 6·3. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%). Light absorption: $\lambda_{max.}$ 205 (ε 45,000), 247 (ε 23,800), and 272 mμ (ε 7600). Karrer and Seyhan (*Helv. Chim.*

Acta, 1950, **33**, 2209—2210) record m. p. 118—119° for the isomeric flav-3-en prepared by lithium aluminium hydride reduction of apigenidin trimethyl ether.

The experimental conditions described above for the preparation of the flav-2-en were adopted after trial experiments with aqueous and anhydrous hydrazine at the b. p. had proved unsatisfactory, although some of the flaven was undoubtedly formed. The modified conditions have the advantage over those of Freudenberg, Fikentscher, and Harder (*loc. cit.*) that a homogeneous solution is soon formed and the product separates from the cold solution in an analytically pure form.

Formation of Apigenidin Trimethyl Ether.—A solution of the flav-2-en (*ca.* 0·02 g.) and dry hydrogen chloride in chloroform (10 c.c.) and benzene (10 c.c.) developed an orange colour slowly and after seven days at room temperature it was filtered from dark brown needles. Recrystallisation from 4N-hydrochloric acid afforded apigenidin trimethyl ether pentahydrate in orange needles, m. p. and mixed m. p. 159—160° (decomp.); the light absorption curve was indistinguishable from that recorded below for an authentic specimen. For analogous conversions see Baker (*J.*, 1929, 1593).

(±)-5 : 7 : 4′-*Trimethoxyflavan* (VI).—(*a*) A solution of 5 : 7 : 4′-trimethoxyflav-2-en (0·0577 g.) in glacial acetic acid (5 c.c.) was shaken with hydrogen at room temperature and pressure over platinum black (*ca.* 0·05 g.). Hydrogen was absorbed rapidly at first (1 c.c. in 2·5 min., 2 c.c. in 7·5, 3 c.c. in 14, 3·5 c.c. in 20 min., 4 c.c. in 1 hour) and the hydrogenation was discontinued after 97 min. (4·1 c.c.; theory 4·6 c.c. at 20°/760 mm.). After filtration from catalyst the solvent was removed by freeze-drying, and crystallisation of the residue from light petroleum (b. p. 40—60°) afforded (±)-5 : 7 : 4′-*trimethoxyflavan* in small prisms, m. p. 105—106° alone and when mixed with the authentic specimen described below (Found: C, 71·4; H, 6·7. $C_{18}H_{18}O_4$ requires C, 72·0; H, 6·7%). Light absorption: $\lambda_{max.}$ 208 (ε 55,200) and 274 mμ (ε 2400). Hydrogenation of the flav-2-en in ethanol was inconveniently slow.

(*b*) An alcoholic solution of apigenidin trimethyl ether pentahydrate (1 g.) (prepared as described below) when shaken with hydrogen at room temperature and pressure over platinum black (*ca.* 0·5 g.) absorbed 56 c.c. (1 mol.) in 3 min. After absorption of the second molecular equivalent of hydrogen, which requires 3 hr., the catalyst was removed and the filtrate was concentrated under reduced pressure. An ethereal solution of the residual oil was washed with aqueous sodium hydroxide and with water, and after removal of the ether the residue separated during spontaneous evaporation of its aqueous-ethanol solution as a buff coloured powder (0·36 g., 50%), m. p. 99—100°. (±)-5 : 7 : 4′-Trimethoxyflavan crystallised slowly from light petroleum (b. p. 40—60°) in small prisms, m. p. 107—108°, and from aqueous methanol in rosettes of larger prisms, m. p. 107—108° (Found: C, 72·0; H, 7·0. Calc. for $C_{18}H_{20}O_4$: C, 72·0; H, 6·7%). The flavan is readily soluble in benzene and in alcohols, moderately soluble in hot light petroleum, and insoluble in water and in aqueous sodium hydroxide. It has a pronounced tendency to separate as an oil from aqueous-alcoholic solutions.

Preparation of Apigenidin Trimethyl ether (VII; R = H).—5 : 7 : 4′-*Trimethoxyflavylium chloride pentahydrate* was obtained in the form of orange needles (70%), m. p. 159—160° (decomp.), by the method of Pratt, Robinson, and Williams (*J.*, 1924, 205) who do not record m. p., yield, or analysis (Found: C, 51·7; H, 6·2. $C_{18}H_{17}O_4Cl,5H_2O$ requires C, 51·1; H, 6·4. Found, after drying *in vacuo* at 110°: C, 64·5; H, 5·3; loss 20·3. $C_{18}H_{17}O_4Cl$ requires C, 65·0; H, 5·2; loss 21·3%). Light absorption: $\lambda_{max.}$ 207 (ε 30,900), 278 (ε 19,850), 326 (ε 4840), and 476 mμ (ε 35,400); in 0·001N-HCl in EtOH: $\lambda_{max.}$ 208 (ε 28,200), 242 (ε 10,600), 278 (ε 21,600), 324 (ε 6300), and 476 mμ (ε 41,300).

(±)-cis-5 : 7 : 4′-*Trimethoxyflavan*-3-*ol*.—3-Hydroxy-5 : 7 : 4′-trimethoxyflavylium chloride trihydrate (1 g.) (prepared as described below) in ethanol (50 c.c.) was hydrogenated at room temperature and pressure over platinum black (*ca.* 0·5 g.). When hydrogenation was complete (4 hr.) the catalyst was removed and the filtrate was concentrated under reduced pressure, to leave a residue which dissolved in ether (charcoal). Removal of the ether, after the solution had been washed with aqueous sodium hydroxide and water, left a colourless viscous residue (A) (*ca.* 0·8 g.) which crystallised slowly at 0° from a mixture of benzene (4 c.c.) and light petroleum (6 c.c.). Recrystallisation from aqueous methanol of this crude material (0·1570 g., 17%), m. p. 97—98° to a turbid liquid clearing at 103°, afforded (±)-cis-5 : 7 : 4′-*trimethoxyflavan*-3-*ol* as a microcrystalline solid which softened at *ca.* 99° and melted to a clear liquid at 105° (Found: C, 68·4; H, 6·4. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%). The m. p. of the racemic compound was unaltered by admixture with (−)-*epi*afzelechin trimethyl ether (m. p. 110°) described above. The infrared absorption curves of the (−)- and the (±)-compound dissolved in carbon tetrachloride showed an exact correspondence. The light absorption of

the (±)-compound was indistinguishable from that of (−)-*epi*afzelechin trimethyl ether: $\lambda_{max.}$ 208 (ε 53,100) and 274 mμ (ε 2200).

The *acetate* of (±)-*cis*-5 : 7 : 4′-trimethoxyflavan-3-ol which separated from aqueous methanol in prisms (0·023 g.), m. p. 123° (Found: C, 67·0; H, 6·2. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%), was obtained by acetylation of part of the material (A). The m. p. of the (±)-acetate was unaltered by admixture with the (−)-*cis*-3-acetoxy-5 : 7 : 4′-trimethoxyflavan, of m. p. 133°, previously described. The infrared absorption curves of the (−)- and the (±)-acetate dissolved in carbon tetrachloride showed an exact correspondence; the carbonyl absorption band occurred at 5·75 μ.

Preparation of Pelargonidin Trimethyl Ether (VII; R = OH).—2-Hydroxy-4 : 6-dimethoxybenzaldehyde (30%), needles, m. p. 70°, was prepared essentially as described by Freudenberg, Fikentscher, and Wermer (*Annalen*, 1925, **442**, 309—322) except for the use of Adams's modification of the Gattermann reaction (Adams and Levine, *J. Amer. Chem. Soc.*, 1923, **45**, 2373), which may account for the lower yield. A solution of the aldehyde (4 g.) and ω-acetoxy-4-methoxyacetophenone (4 g., m. p. 59°) (Tiffeneau, *Compt. rend.*, 1910, **150**, 1182) in ethyl acetate (50 c.c.) and ethanol (10 c.c.) was saturated at 0° with dry hydrogen chloride; after 7 days at room temperature the solution was diluted with dry ether (60 c.c.) and stored at 0° after saturation at this temperature with dry hydrogen chloride. Ten days later the solution was filtered from a *dihydrate* of 3-hydroxy-5 : 7 : 4′-trimethoxyflavylium chloride (3·4 g., 38%), lustrous black prisms, decomp. 213—215° (Found: C, 54·3; H, 5·8; Cl, 13·2; acetyl, 0. $C_{18}H_{17}O_5Cl,2H_2O,0{\cdot}5HCl$ requires C, 53·6; H, 5·4; Cl, 13·2. Found, in a specimen dried to constant weight *in vacuo* at 110°: C, 62·9; H, 5·0; loss 13·3. Calc. for $C_{18}H_{17}O_5Cl$: C, 62·0; H, 4·9; loss, 13·4%). Dilution of the filtrate with dry ether precipitated further crude flavylium salt (*ca.* 4·0 g.). Recrystallisation of the salt (1·0 g.) from 1 : 1 ethanol–concentrated hydrochloric acid (100 c.c.) afforded reddish-orange needles (1·0 g.) consisting of a *hydrate* of pelargonidin 5 : 7 : 4′-trimethyl ether, decomp. 213° (Found: C, 52·8; H, 5·5; Cl, 13·1; OMe, 20·8; loss, at 110° *in vacuo*, 13·6. $C_{18}H_{17}O_5Cl,2{\cdot}5H_2O,0{\cdot}5HCl$ requires C, 52·5; H, 5·5; Cl, 12·8; OMe, 22·6; loss, 15·3%). Light absorption in EtOH containing 0·01M-HCl: $\lambda_{max.}$ 209 (841), 245 (373), 268 (468), 332 (85), 424 (229), and 518 mμ ($E^{1\%}_{1\,cm.}$ 975). Recrystallisation from hydrochloric acid (5%) (Karrer, Widmer, Helfenstein, Hürlimann, Nievergelt, and Monsarrat-Thoms, *Helv. Chim. Acta*, 1927, **10**, 729) afforded a less satisfactory preparation of *pelargonidin trimethyl ether monohydrate*, decomp. 197° (Found: C, 59·1; H, 4·9; Cl, 8·5, 8·6. $C_{18}H_{17}O_5Cl,H_2O$ requires C, 58·9; H, 5·2; Cl, 9·7. Found, in material dried at 110° *in vacuo*: C, 62·2; H, 5·5. Calc. for $C_{18}H_{17}O_5Cl$: C, 62·0; H, 4·9%). Karrer *et al.* (*loc. cit.*) record decomp. 130° for the compound recrystallised in this way, but Professor Karrer remarks that his specimen melts at a much higher temperature, although shrinking markedly at 130° (personal communication). A specimen supplied by Professor Karrer decomposed at 190—192°, and the decomp. point was not lowered on admixture with our materials of decomp. 197° and 213°; the light absorption of his specimen was closely similar to that recorded above.

The *perchlorate* crystallised in dark red needles, decomp. 222—225° (Found: Cl, 8·4. $C_{18}H_{17}O_5Cl$ requires Cl, 8·6%).

Afzelin.—From a fissure about 2 ft. in length in a sample of afzelia a yellow powdery material (25 g.) was removed mechanically. Chromatographic analysis showed that afzelin (kaempferol 3-rhamnoside) (I; R = $C_6H_{11}O_4$) (King and Acheson, *J.*, 1950, 168) is the main component, and that the glycoside is not accompanied by the aglycone, but that two other compounds are present in much smaller amounts. These two compounds, which are only detectable on heavily loaded chromatograms, are dihydrokaempferol (II) and *epi*afzelechin (IV).

Paper Chromatograms.—Paper chromatograms were run by the descending technique on Whatman No. 1 paper with *n*-butanol–acetic acid–water (5 : 1 : 4) (B) and *m*-cresol–acetic acid–water (50 : 2 : 48) (C) as solvents (Bate-Smith, *Biochem. Soc. Symp.*, No. 3, Partition

Substance	Range of R_F values B	C	Colour	Fluorescence in u.v.	Colour with $FeCl_3$	Colour with vanillin–HCl
(−)-*epi*Afzelechin	0·73—0·74	0·40—0·43	—	Faint blue	—	Red
Afzelin	0·82	0·58—0·59	Greenish-yellow	—	Green	—
Kaempferol	0·83	0·54—0·55	Yellow	+	Green	—
Dihydrokaempferol	0·87	0·72—0·73	—	+	Brownish-purple	—
Apigenidin trimethyl ether	0·88 (streak)	—	Orange	—	—	—

Chromatography, **1951**, p. 62). Authentic specimens were used as reference compounds on each chromatogram. The chromatograms were examined in daylight and in ultraviolet light, and then sprayed in turn with alcoholic ferric chloride (1%) and vanillin (*ca.* 0·2% in concentrated hydrochloric acid). Results are tabulated.

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The Preparation of Esters of Alkyl- and Aryl-boronic Acids.

By P. B. BRINDLEY, W. GERRARD, and M. F. LAPPERT.

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Di-*n*-butyl boronate was prepared from *n*-butylmagnesium bromide (1 mol.), or, in better yield, from *n*-butyl-lithium (1 mol.) and tri-*n*-butyl borate. The *n*-octyl reagents and tri-*n*-butyl borate gave *n*-butyl di-*n*-octylboronite as principal product. Owing to the greater ease of hydrolysis of arylboronates, the same method was not practicable for the preparation of esters of phenylboronic acid, but these were obtained in excellent yields by esterification of the acid or anhydride by an azeotropic method, not suitable for the *tert.*-butyl ester. This was obtained by action of phenylboron dichloride on *tert.*-butyl alcohol and pyridine.

DURING investigation of the chemistry of boron esters, a number of esters of alkyl- and aryl-boronic acids, $R'\cdot B(OR)_2$, were required, and owing to the sparsity of information, their preparation had to be examined in detail. By the controlled oxidation of spontaneously inflammable triethylboron, $BEt_3 + O_2 \longrightarrow Et\cdot B(OEt)_2$, Frankland and Duppa (*Proc. Roy. Soc.*, 1859, **10**, 568; *J.*, 1862, **15**, 363) prepared diethyl ethylboronate; but Meerwein and Sönke (*J. prakt. Chem.*, 1936, **147**, 251) stated that it is difficult to obtain the ester free from concurrently formed ethyl diethylboronite and triethyl borate. Johnson and Van Campen (*J. Amer. Chem. Soc.*, 1938, **60**, 121) quantitatively converted tri-*n*-butylboron into the boronate by means of absolutely dry air. Wiberg and Krüerke recently (*Z. Naturforsch.*, 1953, **8**b, 608, 609, 610) obtained dimethyl methylboronate by the reaction $Si(OMe)_4 + Me\cdot BBr_2 \longrightarrow Me\cdot B(OMe)_2 + Si(OMe)_2Br_2$. Khotinsky and Melamed (*Ber.*, 1909, **42**, 3090) obtained certain alkyl esters of phenyl- or *m*-tolyl-boronic acids in unstated yields as intermediates in the preparation of the acids from the arylmagnesium bromide and the borate at 0°. Michaelis and Becker (*Ber.*, 1882, **15**, 180) prepared diethyl phenylboronate by the interaction of ethanol and phenylboron dichloride (prepared from boron trichloride and diphenylmercury). From α-naphthylboron dichloride and sodium methoxide, the corresponding boronate was prepared by Michaelis (*Annalen*, 1901, **315**, 19).

n-Butylmagnesium bromide and tri-*n*-butyl borate gave di-*n*-butyl *n*-butylboronate in 42% yield [see (1)], the boronate being freed from metal alkoxide and unchanged borate (which has a similar b. p.) by taking advantage of the greater ease of hydrolysis of the

$$R'MgHal + B(OR)_3 \longrightarrow R'B(OR)_2 + MgHal\cdot OR \quad (1)$$

$$R'Li + B(OR)_3 \longrightarrow R'B(OR)_2 + LiOR \quad (2)$$

latter. Yields were better (60%) when alkyl-lithium was used in place of the Grignard reagent [see (2)] and a suitable apparatus was designed for this procedure. By either method, tri-*n*-butyl borate and the *n*-octyl reagent afforded mainly *n*-butyl di-*n*-octylboronite, $R_2B\cdot OBu^n$.

Neither method was satisfactory for the direct preparation of esters of phenylboronic acid, because the essential treatment with water to decompose the metal alkoxide also largely hydrolysed the boronate.

In the procedure now described, the phenylboronic acid was deliberately obtained (60%) [see (3)] (Bean and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 4415), and then either

esterified directly (see also Toyssell, *Acta Chem. Scand.*, 1954, **8**, 1779, a paper that appeared since completion of the present manuscript) or first dehydrated, by heating, to the anhydride which was then similarly esterified. The latter procedure very considerably reduced the reaction time. Esterification was by an azeotropic method which led to yields of 80—96% (see Table). Yields of acid were poorer (36%) when phenyl-lithium was used. The procedure was not successful with the *tert.*-butyl ester; but by an alternative scheme (4), which appears to be of general applicability, the ester was obtained in 69% yield.

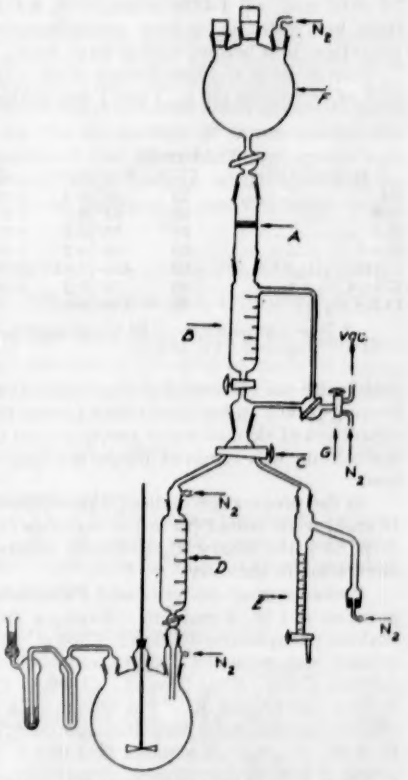
(3) $B(OBu^n)_3 + PhMgBr \xrightarrow{+H_2O} Ph{\cdot}B(OH)_2 \xrightarrow{2ROH} Ph{\cdot}B(OR)_2$

$Ph{\cdot}B(OH)_2 \xrightarrow{-H_2O} Ph{\cdot}BO \xrightarrow{+2ROH} Ph{\cdot}B(OR)_2$

(4) $Ph{\cdot}B(OH)_2 \longrightarrow Ph{\cdot}B(OEt)_2 \xrightarrow{BCl_3} Ph{\cdot}BCl_2 \xrightarrow{2ROH + 2C_5H_5N} Ph{\cdot}B(OR)_2 + 2C_5H_5N,HCl$

Experimental

Addition of n-*Butyl-lithium* (1 *Mol.*) *to Tri*-n-*butyl Borate* (1 *Mol.*).—This order of addition gave the better result, and it was advantageous to remove unchanged lithium from the alkyl-lithium solution before use, and to avoid contact with the atmosphere. Therefore the apparatus shown in the diagram was designed. *n*-Butyl-lithium in ether was prepared in the flask *F*, by the method of Gilman, Beel, Brannen, Bullock, Dunn, and Miles (*J. Amer. Chem. Soc.*, 1949, **71**, 1499) from lithium wire and *n*-butyl bromide at −10° in an atmosphere of nitrogen. For this operation, flask *F* was detached from the main apparatus and supported at bench level. By slight reduction of pressure in *B*, the solution was transferred *via* the coarse sintered-glass filter (*A*) to the reservoir (*B*) and thence by means of a two-way tap (*C*) into a dropping-funnel (*D*) or into a sampling burette (*E*), which permitted the concentration of the *n*-butyl-lithium solution to be determined by Gilman and Haubein's procedure (*ibid.*, 1944, **66**, 1515). Free running through the sintered plate was ensured by periodically reversing the direction of the nitrogen flow through *B* by means of tap *G*. The *n*-butyl-lithium (30·2 g., 1 mol.) in ether was added dropwise to tri-*n*-butyl borate (108 g., 1 mol.) in ether at −60°. After treatment with water, the dried ethereal solution afforded the boronate (56·2 g., 60%), b. p. 108·5°/13 mm., n_D^{20} 1·4169, d_4^{20} 0·8300 (Found: C, 67·5; H, 12·7; B, 4·9. Calc. for $C_{12}H_{27}O_3B$: C, 67·4; H, 12·6; B, 5·1%).



Addition of n-*Butylmagnesium Bromide to Tri*-n-*butyl Borate.*—The Grignard reagent (1 mol.) in ether was added dropwise (1 hr.) with vigorous stirring to the borate (13·9 g., 1 mol.) in ether (100 c.c.) at −70°, whereupon the mixture was poured into ice–water and carefully neutralised with dilute hydrochloric acid. The ethereal layer was washed with water and dried ($MgSO_4$), and the boronate (5·30 g., 42%), b. p. 105°/10 mm., n_D^{20} 1·4180, was obtained. Delay in dealing with the primary reaction mixture resulted in lower yields.

Attempted Preparation of Di-n-*butyl* n-*Octylboronate.*—*n*-Octyl-lithium (42·4 g., 1 mol.) in ether (725 c.c.) was added (1·2 hr.) dropwise with vigorous stirring to tri-*n*-butyl borate (85 g., 1·04 mol.) in ether (600 c.c.) at −60°. After being washed with dilute hydrochloric acid, and

dried, the ethereal solution afforded n-*butyl di*-n-*octylboronite* (60·0 g.), b. p. 80—88°/0·001 mm., n_D^{20} 1·4309—1·4315, which after two redistillations yielded the pure ester, b. p. 84°/0·005 mm., n_D^{20} 1·4312, d_4^{20} 0·8036 (Found: C, 77·7; H, 14·2; B, 3·4. $C_{20}H_{43}OB$ requires C, 77·4; H, 14·0; B, 3·5%).

n-Octylmagnesium bromide (58 g., 1 mol.) in ether was added (2 hr.) dropwise with stirring to tri-*n*-butyl borate (62 g., 1 mol.) in ether at −60°. The mixture was set aside for 18 hr., whereupon the ethereal solution after being washed and dried gave *n*-butyl di-*n*-octylboronite (33 g.), b. p. 80°/0·005 mm., n_D^{20} 1·4288, d_4^{20} 0·824 (Found: B, 3·5%), and *di*-n-*octyl* n-*octylboronate* (10 g.), b. p. 125—132°/0·005 mm., n_D^{20} 1·4409, d_4^{20} 0·842 (Found: C, 75·6; H, 13·2; B, 4·0. $C_{24}H_{51}O_2B$ requires C, 75·4; H, 13·4; B, 2·8%).

Attempted Preparation of Phenylboronates.—Phenyl-lithium (40·8 g., 1 mol.) in ether was added (1·6 hr.) dropwise with stirring to tri-*n*-butyl borate (110 g., 1 mol.) in ether at −60°. After rapid washing, volatile matter was removed from the ethereal portion at 18°/0·1 mm. Phenylboronic acid (12·5 g.), m. p. 206—208° (Found: B, 8·4. Calc. for $C_6H_7O_2B$: B, 8·9%), separated and was filtered off. The filtrate after a number of distillations gave *di*-n-*butyl phenylboronate* (10%), b. p. 97°/0·2 mm., n_D^{17} 1·4800 (Found: B, 4·6. $C_{14}H_{23}O_2B$ requires B, 4·6%). The overall conversion of borate into boronate or boronic acid was 36%.

To the borate (72·3 g., 1 mol.) in ether at −70° was added (3·3 hr.) with stirring phenylmagnesium bromide (57 g., 1 mol.) in ether. After being washed and dried the ethereal solution afforded crude di-*n*-butyl phenylboronate (18·6 g., 25%), which on redistillation had b. p. 70—72°/0·02 mm., n_D^{21} 1·4828 (Found: B, 4·4%), and a solid residue, which after recrystallisation from hot water gave pure phenylboronic acid (12·8 g., 33·4%), m. p. 209—212°. Total conversion into boronic acid or ester, 58·4%.

Esterification of Phenylboronic Acid.—The results are shown in the Table. Phenylboronic acid or anhydride (50 g., 1 mol.) was heated with the appropriate alcohol (3·5 mols.) in a flask

R in $Ph{\cdot}B(OR)_2$	Yield (pure) (%)	B. p./mm.	d_4^{20}	n_D^{20}	Found (%) C	Found (%) H	Found (%) B	Calc. (%) C	Calc. (%) H	Calc. (%) B
Et	73	50°/0·4	0·9540	1·4785	67·3	8·3	6·1	67·5	8·5	6·1
Bu^n	83	94°/0·3	0·9245	1·4751	71·8	9·7	4·7	71·8	9·9	4·6
Bu^i	96	55°/0·2	0·9163	1·4711	71·95	9·98	4·55	71·8	9·9	4·6
Bu^s *	93	49°/0·2	0·9073	1·4658	71·9	10·1	4·6	71·8	9·9	4·6
$CHMe{\cdot}C_8H_{19}^n$ * †	92	119°/0·01	0·8847	1·4666	76·9	11·5	3·0	76·26	11·35	3·1
$CMe_3{\cdot}CH_2$ * †	80	74°/0·2	0·9003	1·4678	73·8	10·7	4·0	73·3	10·4	4·1
$CCl_3{\cdot}CH_2$ * †	96	118°/0·01	—	1·5333 ‡	§	—	2·7	§	—	2·8

* New compounds. † In these experiments Ph·BO was used. ‡ Supercooled. § Found: Cl, 54·5. Required: Cl, 55·3%.

fitted with an efficient fractionating column (Snyder–Schriner type, 30 cm.) provided with a heating-jacket and a total-reflux partial take-off head. This type of column gave an efficient separation of alcohol–water azeotrope and excess of alcohol, but as the hold-up was considerable, the column was removed before the final distillation of the ester and a nitrogen-bubbler was used.

In the preparation of diethyl phenylboronate, the acid (1 mol.), ethanol (6 mol.), and benzene (8 mol.) were heated (24 hr.) to maintain slow distillation of, successively, the ternary azeotrope (b. p. 65°), the binary (C_6H_6–EtOH) azeotrope (b. p. 68°), and finally excess of benzene, before distillation of the ester.

*Preparation of Di-*tert.*-butyl Phenylboronate.*—To *tert.*-butyl alcohol (6·05 g., 2 mol.) and pyridine (7·1 g., 2 mol.) in chloroform (100 c.c.) at −70° was added dropwise (0·4 hr.) with shaking phenylboron dichloride (7·05 g., 1 mol.) in chloroform (20 c.c.). After 36 hr. at 20°, the solvent was removed (20°/15 mm.—20°/1 mm.). *n*-Pentane was added, and pyridinium chloride (7·2 g., 70%) (Found: Cl, 29·6; C_5H_5N, 66·6. Calc. for C_5H_6NCl: Cl, 30·7; C_5H_5N, 68·5%) was filtered off. The filtrate gave the crude ester (8·3 g., 80%) which on redistillation afforded *di*-tert.*-butyl phenylboronate* (69%), b. p. 42°/0·01 mm., n_D^{20} 1·4635, d_4^{20} 0·9053 (Found: B, 4·59. $C_{14}H_{23}O_2B$ requires B, 4·62%). Phenylboron dichloride was prepared by the interaction of diethyl phenylboronate and boron trichloride.

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Interaction of Boron Trichloride with Hydroxy-esters, and the Fission of Carboxylic Esters.

By M. J. Frazer and W. Gerrard.

[Reprint Order No. 6277.]

Interaction of boron trichloride with hydroxy-esters has been studied to reveal the influence of the electron-attracting ethoxycarbonyl group. In common with alcohols of ordinary reactivity (such as *n*-butanol) (Gerrard and Lappert, *J.*, 1951, 1020, 2545) the hydroxy-esters (3 mols.) and boron trichloride (1 mol.) readily afforded the borates (1) in

$$3ROH + BCl_3 \longrightarrow B(OR)_3 + 3HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

good yield. Although they absorb hydrogen chloride (rather more than 1 mol.) they are not permanently altered by it. They do not form a complex with pyridine, thus showing that the ethoxycarbonyl group is insufficiently powerful to compensate for the "back co-ordination" of the oxygen atoms which appears to account for the non-formation of a complex between a trialkyl borate and pyridine (see Colclough, Gerrard, and Lappert, *J.*, 1955, 907).

Because of the intervention of the ethoxycarbonyl group, which gave ethyl alcohol, the borates could not be isolated by azeotropic removal of water after interaction of a hydroxy-ester and boric acid (see Gerrard and Lappert, *Chem. and Ind.*, 1952, 53). The ethoxycarbonyl group also intervened and gave rise to ethyl chloride when attempts were made to obtain the dichloroboronite, $RO{\cdot}BCl_2$, by the interaction of boron trichloride with the borate or with the hydroxy-ester. Fission of the ethoxycarbonyl group was confirmed by the interaction of boron trichloride with ethyl acetate, which appeared to follow the course shown in (2), and with phenyl acetate (reaction 3) (see Colclough *et al.*, *loc. cit.*).

$$EtOAc + BCl_3 \longrightarrow EtOAc,BCl_3 \longrightarrow AcCl + [EtO{\cdot}BCl_2 \longrightarrow EtCl + BCl_3 + B_2O_3] \quad (2)$$

$$PhOAc + BCl_3 \longrightarrow PhOAc,BCl_3 \longrightarrow AcCl + [PhO{\cdot}BCl_2 \longrightarrow BCl_3 + B(OPh)_3] \quad . \quad (3)$$

The first step in the interaction of ethyl acetate and boron trichloride is the formation of a solid complex, stable at 20°. At this stage no permanent selection of mode of fission has been made; for when *n*-octanol (3 mols.) was added, hydrogen chloride (3 mols.), tri-*n*-octyl borate, and ethyl acetate were steadily formed at 20° (reaction 4).

$$EtOAc,BCl_3 + 3ROH \longrightarrow EtOAc + (RO)_3B + 3HCl \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Experimental.—Reagents were mixed dropwise and well shaken.

Preparation of borates. The hydroxy-ester (3 mols.) was added to the trichloride (1 mol.) at −80°. (Similar results were obtained when the order of mixing was reversed.) A white solid was formed, which at room temperature gave hydrogen chloride, quantitatively absorbed in potassium hydroxide. Results are recorded in the Table.

Preparation of borates of ethyl esters of hydroxy-acids.

Hydroxy ester	HCl evolved (mols.)	Yield (%)	B. p./ 0·01 mm.	n_D^{20}	d_4^{20}	Found (%) C	H	B	Calculated (%) C	H	B
Glycollate	3·0	85 *	124°	1·4290	1·160	45·4	6·8	3·28	45·0	7·5	3·38
β-Hydroxypropionate	2·7	88 *	134	1·4331	1·108	49·8	7·5	3·00	49·7	8·3	2·99
Malate	2·6	80 *	180	1·4408	1·167	49·8	6·9	2·07	49·8	7·3	1·87
Lactate	—	86 †	110	1·4215	1·070	49·9	7·6	3·03	49·7	8·3	2·99

* New compounds. † Reagents mixed in chloroform at −10°, or trichloride added to lactate at −80° [also from trichloride–pyridine complex (Gerrard and Lappert, *Chem. and Ind.*, 1952, 53)].

Ethyl glycollate (62 g., 6 mols.) and boric acid (6·2 g., 1 mol.) when heated (150°) under a column, afforded ethyl alcohol (14·4 g., 3 mols.), b. p. 79°, n_D^{18} 1·3649, ethyl glycollate (33 g., 3 mols.), a brown viscous liquid (3·4 g.), b. p. 100°/0·005 mm. (Found: B, 5·5%), and a black

solid (6·7 g.). Likewise at 135° ethyl lactate (47 g., 4 mols.) gave ethyl alcohol (3 mols.) and a brown gum (35·3 g.) (Found : B, 4·7%).

Attempts to prepare dichloroboronites. Ethyl glycollate (1 mol.) was added to boron trichloride (1 mol.) at −80°. At room temperature the white solid evolved gases and became voluminous. During 2 hr. at 20° and 1 hr. at 60° the solid melted, hydrogen chloride and boron trichloride being continuously evolved, as also when distillation at 10 mm. was unsuccessfully attempted. No further progress was made with ethyl lactate or with ethyl malate, although these were examined in some detail.

Triethoxycarbonylmethyl borate (11·88 g., 1 mol.) was added to boron trichloride (13·05 g., 3 mols.) at −80°. The glass-like solid became voluminous at 0° and during 3 hr., at 20°, a condensate (5·4 g.) collected in the attached trap (−80°). A further condensate (5·4 g.) was obtained when the residue (18·85 g.) was kept at 70° for 3 hr. The final residue (12·25 g.) was a brown solid. To the total condensate, pyridine (7·08 g.) was added, whereupon pyridine–boron trichloride (8·9 g., equiv. to BCl_3, 5·3 g.), m. p. 114° (Found : Cl, 53·9. Calc. for $C_5H_5NCl_3B$: Cl, 54·1%) (Gerrard and Lappert, *J.*, 1951, 1020), was formed, and ethyl chloride (5·2 g.), b. p. approx. 12°, distilled into another trap at −80°. Nothing further was learnt from the other borates.

Fission of carboxylic esters by boron trichloride. Ethyl acetate (9·92 g., 1·0 ml.) was added (0·5 hr.) to boron trichloride (13·20 g., 1·0 mol.) at −80°, and the resulting white solid (23·10 g.) did not lose weight at 20° for 18 hr. During the rest of the experiment the reaction flask was connected to a trap at −80°. The solid melted to a brown liquid at 50°, but there was no loss in weight even at this temperature for 2 hr. The mixture was then heated at 100° for 1 hr., whereupon a liquid refluxed, a white solid formed in the flask, and there was a condensate in the trap. Distillation gave a brown fuming solid (6·0 g.) (Found : B, 12·44; easily hydrolysed Cl 31·95%) and acetyl chloride (7·35 g., 83·1%), b. p. 46—48°, which after two redistillations (boron trichloride and acetyl chloride tend to distil together and are only separated with difficulty) gave acetyl chloride (6·75 g.), b. p. 51°, n_D^{20} 1·3890 (Found : Cl, 45·8. Calc. for C_2H_3OCl : Cl, 45·1%). To the trap condensate (9·4 g.) at −80° pyridine (2·9 g., 0·33 mol.) was added. A violent reaction occurred and pyridine–boron trichloride (7·0 g.) was formed. Ethyl chloride (3·3 g., 45·4%), b. p. 12° approx., was distilled into another trap at −80°. The pyridine–boron trichloride, when washed with water and dried, had m. p. 115° (Found : Cl, 54·1. Calc. for $C_5H_5NCl_3B$: Cl, 54·1%).

The ethyl acetate–boron trichloride complex (7·7 g., 1 mol.) was prepared by the addition of the ester (3·3 g., 1 mol.) to boron trichloride (4·4 g., 1 mol.) at −80°. Octan-1-ol (14·7 g., 3 mols.) was slowly added at −80° (0·5 hr.). As the flask was warmed to 20° the solid began to melt and hydrogen chloride was evolved. The mixture was shaken first at 20° for 2 hr. and hydrogen chloride was collected in potassium hydroxide (Found : HCl, 3·9 g. Calc. for 3 mols. : HCl, 4·1 g.), and then at 15°/10 mm. for 1 hr., whereupon ethyl acetate (3·0 g., 91%), b. p. 77°, n_D^{17} 1·3749, collected in a trap at −80°, and the remaining liquid (12·6 g.) gave a forerun (1·1 g.), b. p. 100—162°/0·2 mm., n_D^{20} 1·4301, and tri-*n*-octyl borate (11·25 g., 75%), b. p. 162°/0·2 mm., n_D^{20} 1·4370, d_4^{20} 0·859 (Found : C, 72·2; H, 12·8; B, 2·9. Calc. for $C_{24}H_{51}O_3B$: C, 72·3; H, 12·8; B, 2·7%).

Phenyl acetate (b. p. 82°/12 mm., n_D^{15} 1·5039) (9·60 g., 1·0 mol.) was added (0·33 hr.) to boron trichloride (8·30 g., 1 mol.) at −80°. A white solid (17·9 g.) was formed which after 0·33 hr. at 20°, started to melt, and after 1·33 hr. was completely liquid (16·4 g.). On distillation this gave a mixture of acetyl chloride and boron trichloride (5·70 g.), b. p. 46—51°. After two redistillations acetyl chloride (4·1 g., 74%), b. p. 51°, n_D^{16} 1·3909 (Found : Cl, 46·8. Calc. for C_2H_3OCl : Cl, 45·1%), was obtained. The residue was kept at 180°/50 mm. for 1 hr. and then weighed 7·3 g. It gave triphenyl borate (5·35 g., 79·5%), m. p. 55—57°, b. p. 150°/0·02 mm. (Found : C_6H_5O, 96·7; B, 3·8. Calc. for $C_{18}H_{15}O_3B$: C_6H_5O, 96·3; B, 3·7%), and a black solid (0·6 g.). Ethyl chloride obtained in these experiments was characterised by approximate b. p. and by analysis (Found : Cl, 54·5. Calc. for C_2H_5Cl : Cl, 55·0%).

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The Structure and Ultraviolet Spectrum of Dianthracene

By C. A. Coulson, L. E. Orgel, W. Taylor, and J. Weiss.

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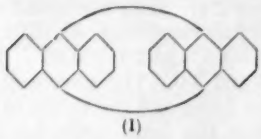
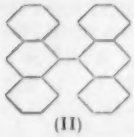
When anthracene is irradiated in solution, a dimer, dianthracene, is formed. It is probable that this dimer plays some part in the self-quenching of fluorescence of anthracene solutions (cf. Weil-Malherbe and Weiss, *J.*, 1944, 541; *Trans. Faraday Soc.*, 1946, **42**, 133). As Weil-Malherbe and Weiss have suggested, an excited anthracene molecule A* can either (*a*) return by direct fluorescence to its ground state according to the equation $A^* \longrightarrow A + h\nu$; or (*b*) form a dimer in a two-stage process $A^* + A \longrightarrow A^+A^- \longrightarrow A_2$, of which the first stage is essentially an electron-transfer. Reaction (*b*) would lead to



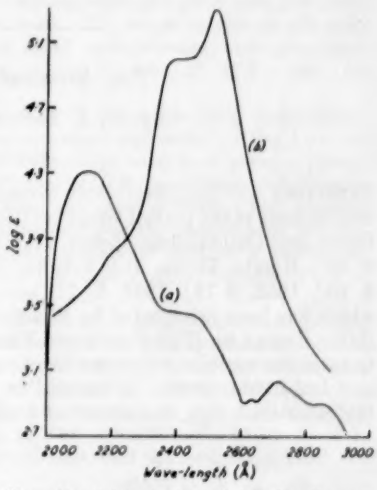
(I)



(II)

(III)

self-quenching of the fluorescence, and can be detected by this means. For this reason the structure of the dimer molecule is of some interest. Hengstenberg and Palacios (*Anales Soc. espan. fis. quím.*, 1932, **30**, 5), from *X*-ray diffraction experiments, were led to the view that the two anthracene units were joined by new bonds connecting their *meso* atoms (I). In order for this to be possible each anthracene molecule would need to fold itself out of a plane around the line joining the *meso* carbon atoms rather like the folding of a book. The other likely possibilities (II and III) were excluded on the grounds that if these molecules were assigned reasonable geometrical shapes and sizes, they would not pack together in the unit cell which was determined by *X*-ray analysis. This somewhat negative evidence has recently been supplemented by Medvedev, Mikhailov, Prikhot'ko, and Kharitonova (*Izvest. Akad. Nauk U.S.S.R.*, Ser. Fiz., 1953, **17**, 715), who irradiated pure 9-methylanthracene in acetone solution and crystallised the resulting dimer. These writers found that its ultraviolet spectrum was entirely different from that of the monomer, and appeared to correspond to a loss of much of the aromatic character of the original monomer. No details of the shape of the spectrum were given, although it should be possible from a study of this spectrum to settle the matter unambiguously.



The ultraviolet spectra of (a) dianthracene and (b) anthracene.

We have therefore prepared the dimer of anthracene itself, by irradiation of anthracene in ethanol. The precipitate was filtered off and recrystallised from ethanol. Subsequently a solution in light petroleum (b. p. 60—80°) (in which it is sparingly soluble) was chromatographed on alumina, and the material eluted with benzene (5-ml. fractions). The solvent was evaporated off under slightly reduced pressure and the residues were dried and then dissolved in alcohol. The ultraviolet spectrum of each fraction was measured on a "Unicam" S.P.500 spectrophotometer. The first fractions showed the familiar peak at 2520 Å, which is due to the anthracene monomer, together with a new peak at 2175 Å and a band showing some vibrational fine structure at 2600—2800 Å. In the later fractions

the peak at 2520 Å grew weaker, and eventually almost disappeared, while the peak at 2175 Å and the band around 2700 Å remained. Collection of fractions was continued until two consecutive fractions gave the same spectrum. The alcohol used as solvent in the measurement of this spectrum was purified by distillation over potassium hydroxide and then refluxing and distillation from magnesium ethoxide. The Figure shows the final curve.

Now if the structure of dianthracene is as in (I) we should expect that the spectral properties of the molecule would resemble those of a superposition of four benzene rings each disubstituted by alkyl groups in *ortho*-positions. The ultraviolet spectra of *o*-dialkylbenzenes, however (see, *e.g.*, the spectrum of *o*-xylene in the Amer. Petrol. Inst. Research Project 44, serial numbers 55, 173), (1) exhibit a peak at about 2120 Å; (2) for this peak have log $\varepsilon_{max.}$ about 3·9; (3) exhibit a band in the region 2600—2800 Å, with vibrational structure showing peaks at 2630 and 2710 Å, no trace of which can be found in the spectrum of anthracene itself; and (4) for this band have log $\varepsilon_{max.}$ about 2·4. Since our model for dianthracene requires that the absorption should be similar to four times that of a dialkylbenzene, the expected values of log $\varepsilon_{max.}$ would be 3·9 + 0·60 = 4·5, and 2·4 + 0·60 = 3·0, respectively. The corresponding values in the figure are 4·3 and 3·0. The agreement in all four respects between the experimental results shown in the figure and the values to be expected from our model leaves no reasonable doubt but that the dimer really has the geometrical structure (I).

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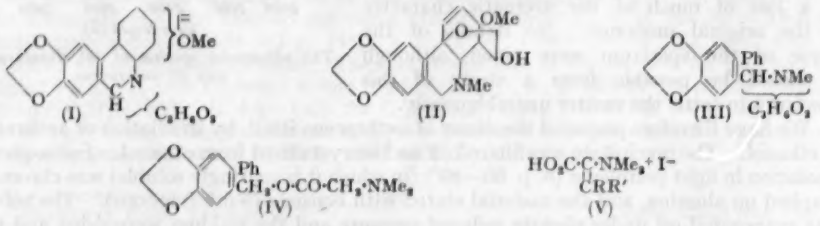
The Structure of Tazettine Methine.

By W. I. Taylor, S. Uyeo, and H. Yajima.

[Reprint Order No. 6183.]

Tazettine was first extensively investigated by Späth and Kahovec (*Ber.*, 1934, **67**, 1501) who arrived at the partial structure (I) for the alkaloid. Kondo and his co-workers (Kondo, Ikeda, and Okuda, *Ann. Report, ITSUU Lab.*, 1950, **1**, 61; Kondo and Ikeda, *ibid.*, 1951, **2**, 55; Kondo, Ikeda, and Takeda, *ibid.*, p. 60; Kondo, Ikeda, and Taga, *ibid.*, 1952, **3**, 65; 1953, **4** 73; 1954, **5**, 72) accumulated much valuable data concerning the base which has been interpreted by Wenkert (*Experientia*, 1954, **10**, 476) leading to the formula (II). Except for (III) (Späth and Kahovec, *loc. cit.*), no structure was specifically assigned to tazettine methine which has been examined more closely by Clemo and Hoggarth (*Chem. and Ind.*, 1954, 1046). It seemed to us however that their results implied the structure (IV) and that, *e.g.*, the action of halogen acids on the methine was S_N2 replacement at



the benzylic carbon atom yielding the corresponding 6-phenylpiperonyl halide and salt of dimethylaminoacetic acid (this observation has been confirmed, see Experimental section). The action of methyl iodide on the methine under vigorous conditions in acetone or ethyl methyl ketone could also be readily explained on this basis; the ketone condenses

with the reactive methylene group of the first-formed methine methiodide which is then converted into 6-phenylpiperonyl iodide and the salt (V) (with acetone R = R′ = Me; with ethyl methyl ketone R = Me, R′ = Et) with which Clemo and Hoggarth's analyses are in good agreement. This sequence of reactions is probably correct since betaine iodide itself does not react with acetone under reflux. The most powerful argument against structure (IV) for tazettine methine was the observation by Späth and Kahovec (*loc. cit.*) that it was optically active. We now find that the methine regenerated from its picrate is optically inactive and that reduction with lithium aluminium hydride affords 6-phenylpiperonyl alcohol and 2-dimethylaminoethanol. The synthesis of the ester (IV) was accomplished by treating 6-phenylpiperonyl alcohol successively with chloroacetyl chloride and dimethylamine in dry benzene to yield (IV) whose infrared and ultraviolet spectra and picrate were identical with those of the natural derivative.

Experimental.—Ultraviolet absorption spectra were taken in 95% EtOH.

Tazettine methine. The methine was prepared according to the directions of Späth and Kahovec (*loc. cit.*) and its picrate purified by many crystallisations from acetone to m. p. 178° (Found: C, 53·3; H, 4·1; N, 10·3. Calc. for $C_{18}H_{19}O_4N,C_6H_3O_7N_3$: C, 53·1; H, 4·1; N, 10·3%). The methine regenerated from its picrate had $[\alpha]_D$ ±0° (*c*, 0·8 in $CHCl_3$); ν_{CO} 1754 cm.$^{-1}$ and in the ultraviolet region $\lambda_{max.}$ 257 and 293 mμ (log ε 3·89 and 3·72) practically identical with data for 6-phenylpiperonyl alcohol.

Reduction of the methine. Tazettine methine (150 mg.) and lithium aluminium hydride (100 mg.) in ether (20 ml.) were refluxed for 3 hr. A little water was added and the precipitated inorganic salts were filtered off. The ethereal filtrate after concentration yielded cubic crystals (82 mg.), m. p. 100—102°, unaltered on further crystallisation, which gave no depression in m. p. on admixture with 6-phenylpiperonyl alcohol. The ethereal mother-liquors were combined and treated with a saturated ethereal solution of picric acid. The resulting picrate (48 mg.) had m. p. 92—94° after three crystallisations from ethyl acetate–ether and was identical with 2-dimethylaminoethanol picrate (Found: C, 37·8; H, 4·6; N, 17·5. Calc. for $C_4H_{11}ON,C_6H_3O_7N_3$: C, 37·7; H, 4·4; N, 17·6%).

Action of hydrochloric acid on the methine. The methine (150 mg.) in 18% hydrochloric acid (2 ml.) was heated on a water-bath; after a few minutes an oil separated. After 1 hr. the cooled mixture was extracted with ether, dried ($CaCl_2$), then evaporated to dryness. Trituration of the residue with light petroleum (b. p. 60—80°) furnished 6-phenylpiperonyl chloride (62 mg.), m. p. 58—59° after further crystallisation from the same solvent. The aqueous acidic solution was evaporated to dryness under reduced pressure and the residue after crystallisation from ethanol yielded dimethylaminoacetic acid hydrochloride (26 mg.), m. p. and mixed m. p. 186—189° (Found: C, 34·6; H, 7·4; N, 10·0. Calc. for $C_4H_{10}O_2NCl$: C, 34·4; H, 7·2; N, 10·0%).

Synthesis of tazettine methine. The reaction product from 6-phenylpiperonyl alcohol (560 mg.) and chloroacetyl chloride (0·2 ml.) was heated for a short time *in vacuo* to remove traces of hydrogen chloride, then covered with benzene (5 ml.) containing dry dimethylamine (200 mg.). After 24 hr. the crystalline hydrochloride was filtered off and converted into the free oily base (450 mg.) which was purified by distillation *in vacuo* at 150°. It formed a picrate, yellow hexagonal plates (from methanol), m. p. 178° (Found: C, 53·1; H, 4·1. Calc. for $C_{18}H_{19}O_4,C_6H_3O_7N_3$: C, 53·1; H, 4·1%), on admixture with the methine picrate.

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Vapour Pressures and Densities of Some Lower Alkylphosphonates.

By GENNADY M. KOSOLAPOFF.

[Reprint Order No. 6221.]

IT was shown earlier (Kosolapoff, *J.*, 1954, 3222) that the dipole moments of dialkyl alkylphosphonates, $R'\cdot PO(OR)_2$, do not, in themselves, provide an adequate basis for the postulation of hindered rotation of the various groups in these esters. However, this subject is of relatively great importance in practive since it bears directly upon the chemical reactivities of such esters (cf. Kosolapoff, *loc. cit.*). In the hope that some of the other physical properties of the esters might afford an insight into this matter, observations were made of the vapour pressures and the densities of six lower members of this family over a range of temperature: esters in which the chain-length is inadequate for screening of the central oxygen (by suitable rotation) would be expected to display greater interaction with the neighbouring molecules than members in which the " onion-shaped " molecule could be attained as one of the configurational states.

The results appear to justify these concepts. When the vapour-pressure data were plotted in the form of log p *versus* $1/T$ (T being in °K), the plots were curvilinear. However, from approximately 140° C to 70—90° C the deviation from the rectilinear form was generally not great, so that a fitting of a straight-line plot could be justified. This fitting, done by the method of least squares, made it possible to calculate the heats of vaporization by conventional methods from the slope of the rectilinear plot $\log p = a + b/T$; this reproduced the experimental values generally within 2%, although it is realized that such a rectilinear representatiom is an oversimplification. The values of the heats of vaporization, thus obtained, are shown in Table 1. The most striking fact about these values is

TABLE 1. *Vapour pressures of esters.*

$Me\cdot PO(OMe)_2$		$Et\cdot PO(OMe)_2$		$Me\cdot PO(OEt)_2$		$Me\cdot PO(OPr^i)_2$		$Et\cdot PO(OEt)_2$		$Pr\cdot PO(OEt)_2$	
(*Vapour pressures in mm.* Hg; *temperatures in* ° C.)											
t	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*
135·0°	190·5	137·0°	168·6	129·0°	112·6	133·0°	114·5	133·5°	97·3	134·0°	59·4
128·0	154·5	128·0	123·6	119·0	80·6	125·0	84·5	125·0	71·8	124·0	37·4
117·0	100·5	118·5	85·1	110·0	56·1	116·0	60·5	116·0	50·3	115·0	24·9
106·0	64·5	108·0	55·6	101·0	35·6	107·0	41·0	105·5	31·3	105·0	14·9
98·0	44·5	98·0	35·6	89·0	22·1	98·0	28·5	95·5	19·3	95·5	7·9
90·0	30·5	88·5	21·1	81·3	14·1	89·0	18·5	85·5	9·3	87·3	3·9
80·5	18·5	78·2	11·1	74·5	9·1	77·0	7·0	76·5	4·3		
70·3	9·7	69·4	5·6	70·0	5·2	70·0	2·0				
63·0	4·9	60·2	1·6								
Calculated constants for the equation $\log p = a + b/T$.											
a	9·0123		9·2569		8·7973		8·5459		8·8670		10·07271
b	−2736·3		−2872·7		−2706·8		−2634·4		−2792·7		−3374·1
Calculated heats of vaporization (*cal. per mole*).											
	12,500		13,100		12,400		12,050		12,800		15,400

the considerable difference between the isomers diethyl propylphosphonate and di*iso*propyl methylphosphonate, the former being a substance in which a complete screening of the PO group by the three chains is possible, and the latter being one in which such screening is impossible on the side of the methyl group. This difference in the heats of vaporization, amounting to some 3300 cal. per mole, obviously cannot be wholly attributable to the possibility of intramolecular screening. It is nevertheless noteworthy that the remaining esters in this group show a very close grouping of the calculated heats of vaporization and one which clusters about the value calculated for di*iso*propyl methylphosphonate. It may be significant that all these esters are structurally incapable of effecting a complete screening of the central PO group by all three chains attached to the phosphorus atom.

The densities of these esters over a range of temperature are shown in Table 2. Plots

of density against temperature (°c) were sensibly linear and afforded a computation of the thermal expansion coefficients, $a = (v_t - v_0)/v_0 t$, and the rates of the change of molar volume with temperature, $(\partial V/\partial t)_p$. The values of a are very nearly identical among the

TABLE 2. *Densities.*

d_4	t	V	d_4	t	V	d_4	t	V
Me·PO(OMe)$_2$			Me·PO(OEt)$_2$			Me·PO(OPr^i)$_2$		
1·1507	30·0°	107·8	1·0406	30·0°	146·2	0·9734	30·0°	185·1
1·1366	42·0	109·2	1·0234	47·0	148·6	0·9619	41·0	187·3
1·1242	53·5	110·4	1·0125	57·0	150·2	0·9547	49·0	188·7
1·1164	60·0	111·1	1·0024	67·0	151·8	0·9428	61·5	191·1
1·1047	71·0	112·3	0·9937	76·0	153·1	0·9313	72·0	193·5
1·0958	79·0	113·2	0·9881	81·0	153·9	0·9238	81·0	195·1
1·0846	89·0	114·4	0·9784	90·0	155·5	0·9144	91·0	197·1
1·0717	100·5	115·8	0·9683	100·2	157·1	0·9050	100·0	199·1
$a = 0·00108$			$a = 0·00110$			$a = 0·00112$		
$(\partial V/\partial t)_p = 0·1126$			$(\partial V/\partial t)_p = 0·1554$			$(\partial V/\partial t)_p = 0·1998$		
Et·PO(OMe)$_2$			Et·PO(OEt)$_2$			Pr·PO(OEt)$_2$		
1·1029	30·0	125·2	1·0158	32·0	163·6	0·9937	30·0	181·3
1·0850	45·0	127·3	1·0008	46·0	166·0	0·9839	40·0	183·1
1·0731	56·0	128·7	0·9888	58·0	168·1	0·9755	48·0	184·7
1·0623	67·0	130·0	0·9826	65·0	169·1	0·9660	57·0	186·5
1·0561	72·5	130·8	0·9746	73·0	170·5	0·9576	68·5	188·2
1·0462	82·0	132·0	0·9642	83·0	172·3	0·9495	77·0	189·8
1·0394	89·0	132·9	0·9580	89·5	173·5	0·9390	88·0	191·9
1·0279	100·0	134·4	0·9473	100·3	175·4	0·9275	99·5	194·3
$a = 0·00108$			$a = 0·00110$			$a = 0·00106$		
$(\partial V/\partial t)_p = 0·1306$			$(\partial V/\partial t)_p = 0·1683$			$(\partial V/\partial t)_p = 0·1864$		

entire group of esters, while the values of $(\partial V/\partial t)_p$ show a progressive increase with the molecular size.

The results obtained, particularly among the measurements of the vapour pressures, may signify some reality of the ideas of partly hindered rotation in the phosphonates (Arbuzov and Vinogradova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1952, 882, 865, 505; 1951, 733; 1947, 459).

Experimental.—The compounds were prepared as described previously (Kosolapoff, *loc. cit.*). Vapour pressures were determined with the original design of the isoteniscope (Smith and Menzies, *J. Amer. Chem. Soc.*, 1910, **32**, 1413) of small volume. This device was agitated during the runs by a flexible tip attached to the mechanical stirrer in the thermostat. The electrically controlled thermostat was kept within 0·1° of the selected temperatures. The pressure readings, made with a mercury manometer, were corrected for temperature, altitude, and latitude. It is realized that the isoteniscope is not reliable at the lower pressures and the last values in Table 1 are not trustworthy; these, of course, were not included in the calculations.

The densities were determined conventionally by means of a pyknometer which had been calibrated with water; the determinations were made with the aid of an electrically regulated thermostat and were probably correct within 0·0002 unit. The molar volumes, V, and the thermal coefficients of expansion were calculated from conventional formulæ.

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The Preparation and Rate of Alkaline Hydrolysis of 2-Acetamidoethyl Thiolacetate.

By F. J. McQuillin and J. Stewart.

[Reprint Order No. 6242.]

Hawkins and Tarbell (*J. Amer. Chem. Soc.*, **1953**, **75**, 2982) reported the rate of hydrolysis of 2-acetamidoethyl thiolacetate by alkali at 0°. It was of interest to extend the temperature range so as to derive the Arrhenius parameters for this reaction.

Hydrolysis was followed by the change in the characteristic thiolacyl absorption at 233 mμ (cf. Cunneen, *J.*, **1947**, **134**; Hawkins and Tarbell, *loc. cit.*; Schwyzer, *Experientia*, **1954**, **10**, 61). 2-Acetamidoethanethiol was found by electrometric titration to have a pK_a value of 9·2. Calculation of rate constants has therefore been based on the equation: $Me{\cdot}CO{\cdot}SR + 2HO^- \longrightarrow RS^- + Me{\cdot}CO_2^- + H_2O$. The results are given in the Table. The activation energy and probability terms have values very similar to those reported for the alkaline hydrolysis (in more or less aqueous acetone) of simple alkyl thiolacetates which do not contain the acylamino-group (Schaefgen, *J. Amer. Chem. Soc.*, **1948**, **70**, 1308; Rylander and Tarbell, *ibid.*, **1950**, **72**, 3021). By use of these values of E and $\log_{10} A$, the

Temp.	Ester (10^{-3} mol. $l.^{-1}$)	$[HO^-]$	$k_{obs.}$ (mol. $l.^{-1}$ $sec.^{-1}$)	$k_{calc.}$ *
22·6°	1·159	6·68	0·128	0·125
27·4	1·183	3·579	0·174	0·177
28·2	1·152	3·88	0·180	0·188
32·5	1·183	3·52	0·258	0·252

* Calc. by using E 12·7 kcal./mole and $\log_{10} A$ 8·5.

rate constant at 0° is calculated as 0·021 in comparison with Hawkins and Tarbell's observed values of 0·0178—0·0192 (*loc. cit.*). It is possible that our value of E may be slightly low, but there may also have been some small difference in the samples of 2-acetamidoethyl thiolacetate used; our material gave $\varepsilon = 4{\cdot}63 \times 10^3$ at 233 mμ, Hawkins and Tarbell give $\varepsilon = 4{\cdot}51 \times 10^3$.

The 2-acetamidoethyl thiolacetate (III) required for these experiments was obtained by acetylation of 2-acetamidoethanethiol (II) which was prepared in good yield from 2-bromoethylammonium bromide and potassium thioacetate. The corresponding thiolbenzoate (IV) was similarly prepared. This route to 2-acetamidoethanethiol avoids the use of ethyleneimine (cf. Kuhn and Quadbeck, *Chem. Ber.*, **1951**, **84**, 844; Wieland and Bokelmann, *Annalen*, **1951**, **576**, 20; Bestian, *ibid.*, **1950**, **566**, 210; Mills and Bogert, *J. Amer. Chem. Soc.*, **1940**, **62**, 1173), and the less convenient route *via* 2-thiothiazoline (Mills and Bogert, *loc. cit.*; Gabriel and Leupold, *Ber.*, **1898**, **31**, 2837). The method was based on the S→N acetyl migration to be expected, under alkaline conditions, of the 2-aminoethyl thiolacetate (I) which is presumably first formed. The reverse migration under acid conditions was not realised; with alcoholic hydrochloric acid, 2-acetamidoethanethiol was hydrolysed to 2-aminoethanethiol.

$$\left.\begin{matrix} {}^{+}NH_3{\cdot}CH_2{\cdot}CH_2Br \\ + \\ Me{\cdot}CO{\cdot}SK \end{matrix}\right\} Br^- \longrightarrow \underset{(I)}{[Me{\cdot}CO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}NH_3]} \longrightarrow \underset{(II)}{NHAc{\cdot}CH_2{\cdot}CH_2{\cdot}SH} \longrightarrow \underset{(III)}{NHAc{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}Ac}$$

$$\underset{(IV)}{NHAc{\cdot}CH_2{\cdot}CH_2{\cdot}SBz} \qquad \underset{(V)}{NHAc{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}SO_2{\cdot}C_6H_4Me} \qquad \underset{(VI)}{C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}OAc}$$

2-Acetamidoethanol is readily available from 2-aminoethanol and ethyl acetate. The *O*-toluene-*p*-sulphonyl derivative (V) by reaction with potassium thioacetate should also lead to 2-acetamidoethyl thiolacetate. On attempting the toluene-*p*-sulphonylation of 2-acetamidoethanol, however, rearrangement was encountered. The product proved to be toluene-*p*-sulphonamidoethyl acetate (VI). The rearrangement must be ascribed to N→O acetyl migration, catalysed by pyridinium ion, which is rapid in comparison with

O-toluenesulphonylation. The yield was low through loss of material, no doubt as the oxazoline.

Experimental.—Hydrolysis of 2-acetamidoethyl thiolacetate. Aqueous sodium hydroxide and a solution of 2-acetamidoethyl thiolacetate, both in oxygen- and carbon dioxide-free water, were brought to equilibrium in the thermostat under oxygen- and carbon dioxide-free nitrogen in a Warburg-type flask with a side limb. After mixing, samples (2 c.c.) were withdrawn and run into 0·01N-hydrochloric acid and the absorptions of the solutions at 233 mμ measured. The residual thiolacetate concentration was calculated, using $\varepsilon = 4{\cdot}63 \times 10^3$.

(i) 22·6°. Ester, $1{\cdot}159 \times 10^{-3}$M; alkali, $6{\cdot}680 \times 10^{-3}$M.

Time (sec.)	287	403	588	648	705	765	846	903	1010	1061
10^4 [Ester]	9·64	8·40	7·46	7·18	6·71	6·63	6·28	5·96	5·56	5·46
10^3k	122	139	131	128	135	127	127	128	126	124

(ii) 27·4°. Ester, $1{\cdot}183 \times 10^{-3}$M; alkali $3{\cdot}579 \times 10^{-3}$M.

Time (sec.)	184	304	374	453	540	631
10^4 [Ester]	10·55	10·07	9·59	9·21	8·74	8·34
10^3k	183	157	170	169	174	175

(iii) 28·2°. Ester, $1{\cdot}152 \times 10^{-3}$M; alkali, $3{\cdot}88 \times 10^{-3}$M.

Time (sec.)	66	127	245	334	418	511	603	701
10^4 [Ester]	11·0	10·6	9·86	9·27	8·77	8·32	7·94	7·83
10^3k	182	176	179	179	184	182	178	176

(iv) 32·5°. Ester, $1{\cdot}183 \times 10^{-3}$M; alkali, $3{\cdot}527 \times 10^{-3}$M.

Time (sec.)	74	142	211	279	343	416	480	583
10^4 [Ester]	11·1	10·5	9·83	9·37	8·88	8·40	8·09	7·73
10^3k	254	255	264	258	260	260	254	238

2-Acetamidoethanethiol. Anhydrous potassium carbonate (14·5 g.) under ethyl alcohol (60 c.c.) was cooled (ice) and treated with thioacetic acid (10 g.) in an atmosphere of nitrogen. After the reaction 2-bromoethylammonium bromide (20 g.) in alcohol (100 c.c.) was added with stirring. The mixture was kept under nitrogen for 12 hr., refluxed for 8 hr., cooled, and filtered. The filtrate, evaporated *in vacuo* under nitrogen and extracted with chloroform, gave 2-acetamidoethanethiol (6·9 g.), b. p. 105°/0·1 mm. (Found: C, 40·7; H, 7·6. Calc. for C_4H_9ONS: C, 40·4; H, 7·5%), characterised by aerial oxidation to di-(2-acetamidoethyl) disulphide, m. p. 87—88° (Kuhn and Quadbeck, *loc. cit.*), and as the *S-p*-nitrobenzyl derivative prepared with *p*-nitrobenzyl chloride and dry potassium carbonate in boiling acetone. *2-Acetamidoethyl p-nitrobenzyl sulphide* formed prisms, m. p. 112°, from benzene (Found: C, 52·4; H, 5·8. $C_{11}H_{14}O_3N_2S$ requires C, 52·0; H, 5·5%).

2-Acetamidoethyl thiolacetate. 2-Acetamidoethanethiol (5 g.) with acetic anhydride (10 c.c.) in dry pyridine (40 c.c.) afforded 2-acetamidoethyl thiolacetate (4·2 g.), b. p. 123—125°/0·1 mm., m. p. 26° (Found: C, 45·2; H, 6·9. Calc. for $C_6H_{11}O_2NS$: C, 44·7; H, 6·8%).

2-Acetamidoethyl thiolbenzoate, prepared by benzoylation of the thiol in pyridine–benzene, formed prisms, m. p. 87—88°, from benzene–light petroleum (Found: C, 59·2; H, 5·9. $C_{11}H_{13}O_2NS$ requires C, 59·2; H, 5·8%).

Hydrolysis of 2-acetamidoethanethiol. The thiol (1 g.) in methanolic hydrogen chloride (8%; 5 c.c.) was gently refluxed (3 hr.), then evaporated *in vacuo*, giving 2-aminoethanethiol hydrochloride, m. p. 67° (from alcohol–ethyl acetate) (Found: C, 21·2; H, 7·2. Calc. for C_2H_8NSCl: C, 21·1; H, 7·1%).

*Reaction of 2-acetamidoethanol with toluene-*p*-sulphonyl chloride.* (*a*) 2-Aminoethanol (12·2 g.) was heated under reflux for 4 hr. with ethyl acetate (50 c.c.) and distilled, to give 2-acetamidoethanol (15 g.), b. p. 120—122°/0·1 mm., n_D^{17} 1·4722 (Found: C, 46·8; H, 8·9. Calc. for $C_4H_9O_2N$: C, 46·6; H, 8·75%).

(*b*) 2-Acetamidoethanol (7 g.) in dry pyridine (25 c.c.), cooled in ice, was treated gradually with toluene-*p*-sulphonyl chloride (16 g.). After 24 hr. the product was isolated (3·5 g.) and identified as 2-toluene-*p*-sulphonamidoethyl acetate, m. p. and mixed m. p. 58—59° (Slotta and Behnisch, *J. prakt. Chem.*, **1932**, **135**, 225, give m. p. 56°) (Found: C, 51·6; H, 6·1. Calc. for $C_{11}H_{15}O_4NS$: C, 51·4; H, 5·8%).

One of us (J. S.) is indebted to the Northumberland County Council for an award.

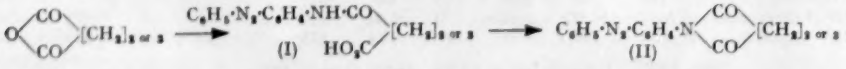
KING'S COLLEGE, NEWCASTLE-UPON-TYNE, 1. [*Received, March 17th*, 1955.]

Isolation and Characterisation of Succinic and Glutaric Acids as p-*Phenylazoanils.*

By H. B. Henbest and T. C. Owen.

[Reprint Order No. 6244.]

Acids of the succinic and glutaric acid type are often formed during the oxidative degradation of organic compounds, but isolation in a pure form is frequently hampered by their water-solubility and by the presence of other acidic products which inhibit crystallisation. It is now reported that these acids may be converted in high yields into coloured, highly crystalline *p*-phenylazoanils (II), which can be readily purified by chromatography on alumina. These derivatives are also readily isolated from less pure samples of the acids (see below).



Conversion of pure succinic and glutaric acids into their anhydrides followed by treatment with *p*-aminoazobenzene in chloroform solution led to the separation of the relatively insoluble anilic acids (I) in 90% yields. Cyclisation of the anilic acids to the anils (II) could be effected in 90% yields by acetyl chloride in chloroform. As an example of a more heavily substituted acid, αα-dimethylsuccinic acid was converted into its *p*-phenylazoanil in 80% overall yield, intermediates not being isolated.

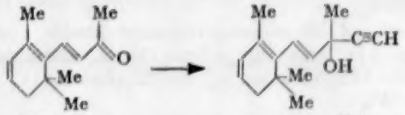
The new derivatives are stable to alumina and give deep yellow bands on a chromatogram and are readily separated; with the compounds studied the order of elution was αα-dimethylsuccino-*p*-phenylazoanil (first), *p*-acetamidoazobenzene, glutaro-*p*-phenylazoanil, succino-*p*-phenylazoanil, and *p*-aminoazobenzene. The use of acetic acid derivatives in the preparation of the cyclic anils led to the possibility that *p*-acetamidoazobenzene might be encountered; it was included therefore in the chromatographic experiments.

Light absorption in chloroform solutions.

	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$		$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$
p-*N*-Dimethylaminoazobenzene *	4100	27,100	Succino-*p*-phenylazoanil	3230	22,000
p-Aminoazobenzene *	3700	25,000	Glutaro-*p*-phenylazoanil	3210	19,100
p-Acetamidoazobenzene	3470	23,400	Azobenzene	3190	11,400
αα-Dimethylsuccino-*p*-phenylazoanil	3250	19,900			

* Data given by Brode, Gould, and Wyman (*J. Amer. Chem. Soc.*, 1953, **75**, 1856).

A further advantage of these derivatives is that small quantities may be estimated by spectrographic methods. Their light-absorption properties are summarized in the Table together with data on related compounds. As expected, progressive acylation of the *p*-amino-group causes shifts of $\lambda_{max.}$ to shorter wavelengths as well as a reduction of intensity.



(III) (IV)

The *p*-phenylazoanil derivatives were first devised in order to identify oxidation products in the vitamin A_2 field. Thus ozonolysis of 3-dehydro-β-ionone (III) (Henbest, *J.*, 1951, 1074) or of the derived (crystalline) ethynyl alcohol (IV) afforded an acidic fraction from which only very small amounts of the expected αα-dimethylsuccinic acid could be isolated by crystallisation. Formation of the *p*-phenylazoanil without isolation of intermediate compounds followed by chromatographic purification gave the αα-dimethylsuccinic acid derivative in reproducible 20—25% yields.

*Experimental.—Succino-*p*-phenylazoanil.* A mixture of succinic acid (6 g.) and acetic anhydride (20 c.c.) was heated at 100° for 30 min. Acetic acid and anhydride were removed under reduced pressure, and the residue in chloroform (20 c.c.) was refluxed with a solution of chromatographically purified *p*-aminoazobenzene (10 g.) in chloroform (20 c.c.) for 30 min. and then cooled to give the virtually pure *anilic acid* (13·5 g.). Crystallisation from ethanol afforded golden needles, m. p. 217° (decomp.) (Found: C, 64·4; H, 4·9; N, 14·3. $C_{16}H_{15}O_3N_3$ requires C, 64·65; H, 5·1; N, 14·15%). A mixture of the anilic acid (1·1 g.) and acetyl chloride (30 c.c.) was heated under reflux until the acid dissolved. Removal of the solvent under reduced pressure gave a product that was chromatographed on alumina (P. Spence, grade H, 100 g.). The single yellow band was eluted with benzene–ether (3 : 1) to give the *anil* (0·9 g.); crystallisation from ethanol yielded pure material, m. p. 214° (Found: C, 69·0; H, 4·8; N, 15·3. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·05%). Dehydration of the anilic acid by heating it at 260° under reduced pressure (20 mm.) for 30 min. gave a dark brown product, which afforded a 50% yield of pure anil on chromatography.

*Glutaro-*p*-phenylazoanil.* The anilic acid was obtained in over 90% yield from glutaric anhydride (1·4 g.) and *p*-aminoazobenzene (2·61 g.) by the procedure given above. Crystallisation from aqueous acetone afforded an *acid*, m. p. 190—192° (Found: C, 66·0; H, 5·8; N, 13·75. $C_{17}H_{17}O_3N_3$ requires C, 65·6; H, 5·5; N, 13·5%). Cyclisation of the anilic acid by acetyl chloride gave a 90% yield of the *anil*, m. p. 219° (Found: C, 69·7; H, 5·6; N, 14·3. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·2; N, 14·35%).

*αα-Dimethylsuccino-*p*-phenylazoanil.* αα-Dimethylsuccinic acid (1 g.) and acetic anhydride (10 c.c.) were heated at 100° for 30 min. Removal of solvent at 80°/20 mm. gave the cyclic anhydride as a yellow oil, which was heated under reflux with a solution of pure *p*-aminazobenzene (1·34 g.) in chloroform for 30 min. The solvent was removed under reduced pressure and the mixture of anilic acids treated with acetyl chloride as above. Chromatography of the product gave the crystalline *anil* (1·6 g., 80%), m. p. 136° (from aqueous ethanol or aqueous acetic acid) (Found: C, 70·4; H, 5·45; N, 14·0. $C_{18}H_{17}O_2N_3$ requires C, 70·35; H, 5·6; N, 13·7%).

Oxidation of 3*-dehydro-*β*-ionone* (III). The ketone (0·44 g.) in carbon tetrachloride (5 c.c.) at 0° was treated with ozonised oxygen (*ca.* 5%; 100 c.c./min.) for 1 hr., during which a gummy ozonide separated. Acetic acid (10 c.c.) was added to dissolve the gum and ozonisation was continued for a further hour. After addition of 5N-sulphuric acid (1 c.c.) the solution was evaporated to about 6 c.c. under reduced pressure. A hot solution of sodium permanganate (1 g.) in 5N-sulphuric acid (25 c.c.) was then added, and the mixture allowed to cool to room temperature during 2 hr. After treatment with sulphur dioxide, the solution was extracted 10 times with ether to yield a semicrystalline acid (0·3 g.), which was treated as above to give αα-dimethylsuccino-*p*-phenylazoanil (0·17 g., 25%), m. p. and mixed m. p. 136°. This procedure gave reproducible yields of anil; if the permanganate treatment was omitted the yield of anil was less than 10%.

Preparation and oxidation of the ethynyl alcohol (IV). Lithium acetylide was prepared by addition of finely cut lithium (1 g.) to a solution of acetylene in liquid ammonia (200 c.c.) in a Dewar vessel. A stream of purified acetylene was passed through the stirred liquid for 20 min. and was continued while a solution of 3-dehydro-β-ionone (15 g.) in dry ether (50 c.c.) was added slowly. Stirring and passage of acetylene were continued for 3 hr., then ammonium chloride (15 g.) was added, and the product was isolated with ether after evaporation of ammonia. Distillation under reduced pressure gave a mixture of alcohol and unchanged ketone which were separated by chromatography on alumina. Distillation gave the pure *alcohol* (5·5 g.), m. p. 31° (Found: C, 83·1; H, 9·25. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%). Ultraviolet light absorption in EtOH; $\lambda_{max.}$ 2860 Å (ε 8400).

Oxidation of this alcohol (1 g.) as described for 3-dehydro-β-ionone gave αα-dimethylsuccino-*p*-phenylazoanil (0·35 g., 23%), m. p. and mixed m. p. 136°.

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THE UNIVERSITY, MANCHESTER, 13. [*Received, March 17th*, 1955.]

p-*Phenylazomaleinanil: A Reagent for Conjugated Dienes.*

By P. Nayler and M. C. Whiting.

[Reprint Order No. 6245.]

p-Phenylazoanils of substituted succinic and glutaric acids (Henbest and Owen, preceding note) are convenient derivatives for the characterisation of these acids. By appropriately modifying the acylation conditions, the corresponding derivative of maleic acid has now been obtained; since maleinanil and its analogues have not been conveniently obtainable hitherto, the method described may be of general value. The *p*-phenylazoanil, however, is particularly useful in that it undergoes Diels–Alder reactions with conjugated dienes to give coloured adducts which can be separated from unchanged reagent, and presumably from each other, by chromatography on alumina with particular ease because of their strong colour. The adducts are high-melting and crystallise well, while the large weight factor is an additional advantage.

Ultraviolet absorption spectra of the adducts and reagents in chloroform are tabulated below. Intensities are so consistent—excluding the *cyclo*pentadiene adduct, which is exceptionally strained—that the reagent could be used for estimating the molecular weight of an unknown diene.

	$\lambda_{max.}$ (Å)	ε	*p*-Phenylazomaleinanil adduct with :	$\lambda_{max.}$ (Å)	ε
p-Phenylazomaleinanilic acid	3600	22,500	Butadiene	3250	22,700
Cf. *p*-acetamidoazobenzene...	3470	23,400	*cyclo*Pentadiene	3240	24,000
p-Phenylazomaleinanil	3280	22,400	*cyclo*Hexadiene	3250	22,900
			Cosmene (bis-adduct)	3280	45,100
			Cf. *p*-phenylazosuccinanil	3230	22,000

The *p*-phenylazoanils of succinic and maleic acid and the four adducts prepared all showed strong infrared bands at 683 ± 2 and 771 ± 6 cm.$^{-1}$ and one or more in the 830—855-cm.$^{-1}$ region. In addition that from butadiene showed bands at 670, 697, and 898 cm.$^{-1}$, that from *cyclo*pentadiene at 718 cm.$^{-1}$ and that from *cyclo*hexadiene at 708 and 808 cm.$^{-1}$. None absorbed intensely between 900 and 1000 cm.$^{-1}$ where vinyl and *trans*-CH=CH-groupings have characteristic bands. The possibilities of structural diagnosis in this region, and the advantages of observing the spectra of readily isolated solids, are obvious. Numerous other bands consistent with the assigned structures but without diagnostic significance were observed.

Experimental.—p-*Phenylazomaleinanilic acid.* Maleic anhydride (5 g.) in chloroform (50 c.c.) was added to a solution of *p*-aminoazobenzene (10 g.) in chloroform (70 c.c.). After 1 hr. at 20° the precipitate was filtered off, washed with ether until the washings were colourless, dried, and added to sodium carbonate solution (100 c.c., 10%). The mixture was stirred until the pink colour had changed to yellow, then filtered; the residual solid was washed repeatedly with ether to remove *p*-aminoazobenzene, dissolved in hot water, and acidified with hydrochloric acid; the precipitated acid was washed with water until the washings were no longer strongly acid to litmus, then once with ethanol, and dried at room temperature, giving the *anilic acid* (11 g., 73%) as pale orange needles, m. p. 215° (Found: C, 65·2; H, 4·9; N, 14·2. $C_{16}H_{13}O_3N_3$ requires C, 65·1; H, 4·5; N, 14·25%). Less carefully purified material consistently gave unsatisfactory results on dehydration.

p-*Phenylazomaleinanil.* The above anilic acid (9 g.) was stirred at 80° with acetic anhydride (100 c.c.) until it dissolved. On cooling, a solid separated which, crystallised from benzene, gave the *anil* (6·5 g., 77%) as orange needles, m. p. 162° (Found: C, 69·55; H, 3·85; N, 15·5. $C_{16}H_{11}O_2N_3$ requires C, 69·3; H, 4·0; N, 15·15%).

Diels–Alder adducts. These were prepared by treating a solution of the anil (740 mg.) in benzene (80 c.c.) with the diene (160—200 mg.) at 20° for 18 hr., evaporation, and chromatography on neutral alumina (200 g.; Peter Spence, Ltd., Grade "H"). Elution of the main band with benzene containing 10% of ether and crystallisation from benzene–light petroleum gave the adduct. Thus buta-1 : 3-diene gave the p-*phenylazoanil* of *cyclo*hex-4-ene-1 : 2-dicarboxylic acid in 55% yield, as needles m. p. 174°, depressed to *ca.* 140° on admixture with

the reagent (Found: C, 72·3; H, 5·05; N, 12·45. $C_{20}H_{17}O_3N_3$ requires C, 72·5; H, 5·15; N, 12·7%): *cyclo*pentadiene gave the *adduct* of 3 : 6-*endo*methylene*cyclo*hex-4-ene-1 : 2-dicarboxylic acid (65%), m. p. 176—177° (Found: C, 73·3; H, 4·85; N, 11·55. $C_{21}H_{17}O_3N_3$ requires C, 73·45; H, 5·0; N, 12·25%); and *cyclo*hexa-1 : 3-diene gave the *adduct* of 3 : 6-*endo*ethylene-*cyclo*hex-4-ene-1 : 2-dicarboxylic acid (50%), m. p. 191—192° (Found: C, 73·7; H, 5·3; N, 11·55. $C_{22}H_{19}O_3N_3$ requires C, 73·95, H, 5·35; N, 11·75%).

A more complex diene, 2 : 7-dimethylocta-1 : 3 : 5 : 7-tetraene ("cosmene;" Nayler and Whiting, *J.*, 1954, 4006) (160 mg.) and the anil (840 mg.) in dry benzene (80 c.c.) were heated to 50° for 5 hr. in nitrogen. Chromatography on alumina (200 g.; Grade "H") gave (*a*) the unchanged reagent (300 mg.), m. p. and mixed m. p. 162—163°, and (*b*), by elution with ether, an adduct, m. p. 138—139° after crystallisation, depressed to *ca.* 120° on admixture with the reagent (Found: C, 72·3; H, 4·7; N, 11·35. Calc. for $C_{42}H_{38}O_4N_6$: C, 73·25; H, 5·25; N, 12·2%). Essentially this was the bis-*p*-phenylazoanil of 2 : 3′-dimethyldi*cyclo*hex-2-enyl-4 : 5 : 4′ : 5′-tetracarboxylic acid, but the tetraene rapidly absorbs oxygen, and impurities containing additional oxygen are evidently retained by the adduct in small amount.

We thank Professor E. R. H. Jones, F.R.S., for his interest, and the Department of Scientific and Industrial Research for a Maintenance Grant to one of us (P. N.).

THE UNIVERSITY, MANCHESTER, 13. [*Received, March 17th*, 1955.]

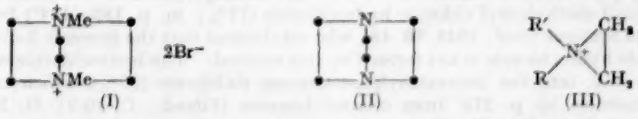
The Production of 1 : 4-*Dialkylpiperazines by the Thermal Decomposition of* 1 : 1 : 4 : 4-*Tetra-alkylpiperazinium Salts.*

By J. I. G. CADOGAN.

[Reprint Order No. 6310.]

THE thermal decomposition of quaternary ammonium halides to give tertiary amines and the corresponding alkyl halide has received considerable attention (Hurd, "Pyrolysis of Organic Compounds," Chemical Catalogue Co., New York, 1929, p. 317). The reaction has not however been exploited as a means of preparation of 1 : 4-dialkylpiperazines. Hromatka and Kraupp (*Monatsh.*, 1951, **82**, 880) and McElvain and Bannister (*J. Amer. Chem. Soc.*, 1954, **76**, 1126) noted that compounds related to 1 : 4-dialkylpiperazines can be obtained by the pyrolysis of quaternary halides. The former workers obtained 1 : 4-diaza*bicyclo*[2 : 2 : 2]octane (II) from the decomposition of the diquaternary salt (I), while the latter similarly obtained hexahydro-1 : 4-dimethyl-1 : 4-diazepine (1 : 4-dimethylhomopiperazine) from its dimethobromide. These reactions are similar to those described in this Note.

Several 1 : 1 : 4 : 4-tetra-alkylpiperazinium dihalides have been prepared and their pyrolysis products studied. All the dichlorides investigated gave the 1 : 4-dialkylpiperazine and alkyl chloride smoothly in 72—88% yield at atmospheric pressure. A lower yield of the base was obtained from the dibromides under comparable conditions,



(I) (II) (III)

owing to the greater ease of recombination of the alkyl bromide and base. Further, a steric effect appears to be operative, since 1 : 1 : 4 : 4-tetramethylpiperazinium dibromide gave a very low yield (10%) of 1 : 4-dimethylpiperazine, whereas 1 : 4-diethyl-1 : 4-dimethylpiperazinium dibromide, under comparable conditions, gave a much higher yield of a mixture of 1 : 4-diethyl- and 1 : 4-dimethyl-piperazine. The method, when applied to the chlorides, is one of synthetic value, and its extensions are readily apparent.

The tetra-alkylpiperazinium dichlorides were prepared by the dimerisation of the corresponding 2-dialkylaminoethyl chlorides in ethanol. Many workers (Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 519; Bartlett, Ross, and Swain, *J. Amer. Chem. Soc.*, 1947, **69**, 2971; Hay, Thompson, and Winkler, *Canad. J. Res.*, 1948, **26**, *B*, 175) have postulated that this type of reaction proceeds through the ethyleniminium ion (III), although the absolute mechanism still appears to be in doubt. Thus 2-dimethylamino-1-methylethyl chloride might give 1 : 1 : 2 : 4 : 4 : 5- and/or 1 : 1 : 2 : 4 : 4 : 6-hexamethylpiperazinium dichloride. The pyrolysis of this dimerisation product could therefore give 1 : 2 : 4 : 5- and/or 1 : 2 : 4 : 6-tetramethylpiperazine. Abderhalden and Haas (*Z. physiol. Chem.*, 1925, **149**, 94) obtained the former as a syrup (dimethiodide, m. p. 250°), while Pope and Read (*J.*, 1914, **105**, 219) describe the mono- and the di-methiodide (m. p. 227° and 241°) of the latter. Our product gave a monomethiodide, m. p. 251°.

Experimental.—Solids, which were all colourless, were dried at 100°/10 mm. over P_2O_5 before analyses and m. p. determinations.

1 : 1 : 4 : 4-*Tetraethylpiperazinium dichloride.* 2-Diethylaminoethyl chloride hydrochloride (0·5 mole) was added to a vigorously stirred ice-cold mixture of water (500 ml.) and ether (250 ml.), the mixture was basified with solid potassium carbonate, and the layers were quickly separated. The ether layer was dried ($MgSO_4$) and removal of the solvent left the base as a yellow oil. This was boiled under reflux with ethanol (250 ml.) for 3 hr., 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride separating as plates which, recrystallised from methanol–acetone (yield 80%), had m. p. >300°.

2-Ethylmethylaminoethyl bromide hydrobromide, prepared in 85% yield from 2-ethylmethylaminoethanol (cf. *Org. Synth.*, **18**, 13), similarly gave the 1 : 4-diethyl-1 : 4-dimethylpiperazinium dibromide (65%), m. p. 295° (from aqueous ethanol) (Found : C, 35·8; H, 7·5. Calc. for $C_{10}H_{24}N_2Br_2$: C, 36·15; H, 7·3%).

1 : 1 : 4 : 4-Tetramethylpiperazinium dibromide, prepared by the condensation of ethylene dibromide with *NNN'N'*-tetramethylethylenediamine in ethanol in 83% yield, had m. p. >330° (from aqueous ethanol).

1 : 1 : 4 : 4-*Tetra-n-propylpiperazinium dichloride.* Ethylene oxide (40 g.) was led into di-*n*-propylamine (101 g.) in a flask fitted with a condenser containing methanol–solid carbon dioxide. There was no reaction, even at 40°, until N-hydrochloric acid (20 ml.) was added (cf. Biel, *J. Amer. Chem. Soc.*, 1949, **71**, 1308). The mixture became dark and was kept at 60° for 2 hr. after the initial reaction had subsided. After being cooled, the organic layer was dried ($MgSO_4$) and fractionated. Di-*n*-propylamine (25%) was recovered, and 2-di-*n*-propylaminoethanol (n_D^{25} 1·4375; 75% based on amine consumed) was collected at 90—92°/20 mm. Burnett *et al.* (*J. Amer. Chem. Soc.*, 1937, **59**, 2248) give n_D^{20} 1·4402.

The alcohol was converted into 2-di-*n*-propylaminoethyl chloride hydrochloride by the action of excess (1·4 mol.) of thionyl chloride in dry benzene at 0°. The free base was isolated and converted as described above into the tetra-alkylpiperazinium salt, which was recrystallised to constant m. p. (295°) from ethanol–ethyl acetate, forming needles (51%).

2-Di-*n*-butylaminoethanol (68%; b. p. 104°/10 mm., n_D^{25} 1·4422; Burnett *et al.*, *loc. cit.*, give n_D^{20} 1·4444), from di-*n*-butylamine and ethylene oxide, similarly (thionyl chloride in chloroform, etc.) gave 1 : 1 : 4 : 4-*tetra-n-butylpiperazinium dichloride monohydrate* (47%), m. p. 239° (from aqueous ethanol–ethyl acetate) (Found : C, 60·1; H, 11·8. $C_{20}H_{44}N_2Cl_2.H_2O$ requires C, 59·8; H, 11·5%).

Hexamethylpiperazinium dichloride. 1-Dimethylaminopropan-2-ol was converted into 2-dimethylamino-1-methylethyl chloride hydrochloride (71%; m. p. 183—184°) by the method of Schultz and Sprague (*ibid.*, 1948, **70**, 48), who established that the isomeric 2-dimethylaminopropyl chloride hydrochloride is not formed by this method. The hydrochloride was converted, in the usual way, into the hexamethylpiperazinium dichloride (65%), which crystallised as hygroscopic needles, m. p. 275° from ethanol–benzene (Found : C, 49·9; H, 9·8. Calc. for $C_{10}H_{24}N_2Cl_2$: C, 49·4; H, 9·95%).

Dry distillation of tetra-alkylpiperazinium salts. The salt was gently warmed with a naked flame until decomposition began. Slight suction was maintained in order to draw the volatile alkyl halides into a cold trap (carbon dioxide–acetone), thus reducing the possibility of recombination of the halide and dialkylpiperazine. This tendency is very slight in the case of the alkyl chlorides, but increases if the halogen is bromine. In all cases tabulated below, the decomposition was very smooth, complete volatilisation of the piperazinium dichlorides being achieved. The

base was collected in a cold receiver and was usually yellow. It was fractionated from potassium hydroxide and a portion was converted into the dimethiodide.

Piperazinium salt $R_2N(<[CH_2]_2>)_2NR_2X_2$		Alkyl in 1 : 4-dialkyl-piperazine	B. p./ 10 mm.	n_D^{25}	Yield (%)	Analyses (%) * Base		Dimethiodide		M. p.
R	X					C	H	C	H	
Et	Cl	Et	68°	1·4520	88	67·2	12·6	28·2	5·34	240° [a]
						67·5	12·8	28·2	5·68	
Pr^n	Cl	Pr^n	84	1·4514	80	70·3	12·8	31·1	6·35	228 [b]
						70·5	13·0	31·4	6·21	
Bu^n	Cl	Bu^n	112 [c]	1·4542	72	72·5	13·1	34·8	6·64	215 [d]
						72·7	13·2	35·0	6·69	
Me	Br	Me	130/ 760 mm.	1·4448	10	62·8	12·2	24·0	5·1	310 [e]
						63·1	12·4	24·1	5·1	
Hexamethyl dichloride		Me_4	62	1·4522	87	67·4	12·8	37·6	7·2 [f]	251 [f]
						67·6	12·8	38·0	7·3	

* Upper rows = Found; lower rows = Calc.
[a] Smith, Curry, and Eifert (*J. Amer. Chem. Soc.*, 1950, **72**, 2969), m. p. 240°. [b] Smith *et al.* (*loc. cit.*), m. p. 227°. [c] Forsee and Pollard (*ibid.*, 1935, **57**, 1788), b. p. 195°/12 mm. [d] Smith *et al.* (*loc. cit.*), m. p. 213°. [e] Mann and Senior (*J.*, 1954, 4476), m. p. 310°. [f] Monomethiodide.

The base obtained from 1 : 4-diethyl-1 : 4-dimethylpiperazinium dibromide gave fractions boiling over a range. Analysis of the combined fractions indicated that the product was a mixture of 1 : 4-diethyl- and 1 : 4-dimethyl-piperazine. Infrared analysis of the basic fraction and the alkyl halide confirmed this conclusion.

Microanalyses were carried out by Mr. F. E. Charlton and Mrs. B. Coddington, and the infrared determinations were by Mr. L. C. Thomas. This work was carried out during the tenure of a Civil Service Research Fellowship, and is published by permission of the Chief Scientist, Ministry of Supply.

Chemical Defence Experimental Establishment,
Porton, Wilts.

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Some Problems in the Chemistry of the Hemicelluloses.

FOURTEENTH PEDLER LECTURE, DELIVERED AT THE UNIVERSITY COLLEGE OF NORTH WALES, BANGOR ON THURSDAY, FEBRUARY 24TH, 1955, AND BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE, ON MARCH 17TH, 1955.

By E. L. HIRST.

IT is now generally accepted that in the cell walls of plants the fundamental skeletal substance consists mainly of α-cellulose, the long thread-like macromolecules of which are arranged in bundles. Within these bundles the free hydroxyl groups of the 1 : 4′-linked β-glucopyranose residues serve to align the cellulose molecules by hydrogen bonding into an organised structure which in parts is so well ordered that it displays crystallinity, whilst in others a looser and more amorphous arrangement is found. Few cells, however, possess a cell wall consisting, as is the case with the cotton hair, almost entirely of cellulose. In most cases, more especially with lignified material, the cellulose bundles are embedded in an amorphous mass of lignin and polysaccharide material, giving a strong and rigid structural element, for which a crude analogy can be found in reinforced concrete. In recent investigations by Rånby[1] and his collaborators in Sweden evidence to this effect has been obtained by the application of the electron microscope to cell-wall materials which had been disintegrated by ultrasonic vibrations. The exact nature of the association in the cell wall between the lignin, the amorphous mass of non-cellulosic carbohydrate material, and the true cellulose is not yet known, but many methods have been derived for the removal of the lignin from the carbohydrates. This can be effected, for instance, by mild treatment with chlorine or sodium chlorite which renders the lignin water-soluble and leaves a so-called holocellulose from which the non-cellulosic constituents can be extracted by aqueous alkali. These materials, for want of a better name, are referred to as hemicelluloses. Their molecular structure is the main theme of the present lecture. In general the hemicellulose fraction contains a number of different polysaccharides, and several kinds of sugar residues are concerned in their molecular architecture, notably D-xylose, L-arabinose, D-galactose, L-rhamnose, D-mannose, D-glucuronic acid, 4-*O*-methyl-D-glucuronic acid, and possibly D-galacturonic acid. Their function is probably to give strength and rigidity to the cell walls. They are therefore cell-wall polysaccharides, but it is not the case that all polysaccharides of this type associated with the cell wall have the same function. Many substances in this group, some of which will be mentioned later, appear rather to be concerned with metabolic processes.

Despite frequent attempts no satisfactory classification of the hemicellulose group has yet been proposed. This is due largely to the difficulties inherent in separating in a pure state the complex mixture of macromolecules of which the group is composed. Usually several molecular species occur in admixture with each other, and one of the major needs of this branch of carbohydrate chemistry is the development of new and powerful methods of fractionation. Advantage can sometimes be taken of special properties, such as the formation of an insoluble copper complex, but the ordinary methods of fractional precipitation or fractional dissolution are of little avail. It may well be that new developments in the technique of ionophoresis will be of assistance, and recently it has been shown by Preece and his collaborators[2] that for certain types of hemicellulose mixtures fractional precipitation by ammonium sulphate is effective.

It follows that much of the exploratory work in this field has been carried out on complex mixtures, examination of which can at best reveal only very general structural features. In this lecture, however, I propose to limit discussion essentially to the chemistry of those hemicellulosic materials which have been separated in a reasonably pure and homogeneous condition. The number of these is steadily increasing and from a study of their structure a general picture of structural relationships within the group is gradually emerging. These studies require the use of all the established methods employed in the polysaccharide field, and additional complications are encountered owing to the occurrence of several sugar residues in one and the same molecule. The question of the order in which these residues are arranged is now important and the problem becomes formally very similar to that of assigning a detailed molecular structure to a protein.

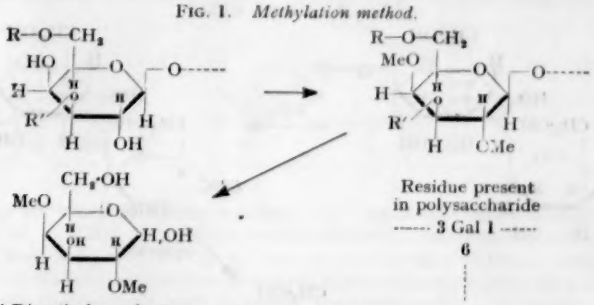
Hydrolysis with acid, followed by qualitative and quantitative chromatographic analysis,

[1] Rånby, Inaugural Dissertation, Inst. Phys. Chem., Uppsala, 1952.

[2] Preece and Mackenzie, *J. Inst. Brewing*, 1952, **58**, 353, 457; Preece and Hobkirk, *ibid.*, 1953, **59**, 385; 1954, **60**, 490.

gives the nature of the sugar residues present in the macromolecule and the proportions in which they are present. In passing, it may be emphasised that within the last few years the development of chromatographic techniques has opened up entirely new horizons in carbohydrate chemistry, and without these new methods the greater part of the work I am describing in this lecture would have been quite impossible. The methylation procedure, despite the 50 years which have elapsed since its first use by Purdie and Irvine, remains one of the most powerful

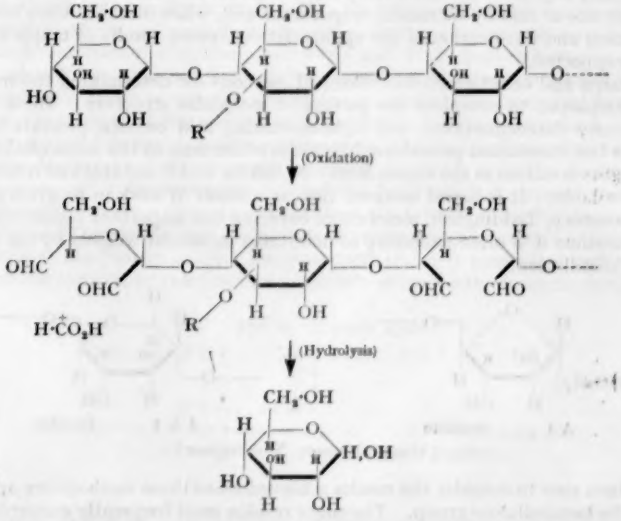
FIG. 1. *Methylation method.*



2 : 4-Dimethyl-D-galactose.

of weapons and by its use, as illustrated for one residue of a polysaccharide in Fig. 1, the mode of linkage of each residue in the molecule can be ascertained. But this method reveals neither the order of the residues nor the nature of the glycosidic links by which the individual sugar units are joined together.

FIG. 2. *Periodate oxidation.*

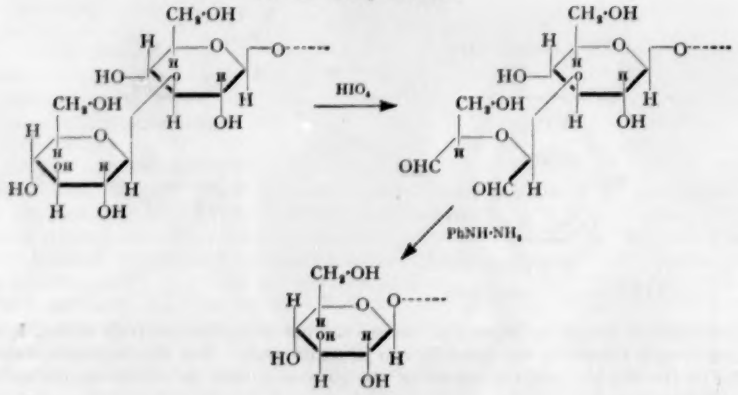


Insight into the order in which the residues occur is now being increasingly obtained by use of the method of partial hydrolysis. Fragments containing from two to eight or more sugar residues can be separated by chromatography on columns of charcoal–Celite, starch granules or other materials and the structures of these break-down products can be determined by standard methods.

Much useful information can be derived from a study of the action of periodate ions on the macromolecules. As indicated in Fig. 2, end-group determinations, the nature and the number of the residues so linked that they are not attacked by periodate, and the proportion of residues

giving rise to a dialdehyde can all be dealt with in this way. By the use of Barry's extension [3] of the procedure polysaccharides containing 1 : 3′-linked residues can sometimes be broken down one residue at a time (see Fig. 3), and the method has recently been still further developed by Barry who has found that insoluble derivatives of the polyaldehyde can be obtained by reaction with *iso*nicotinhydrazide or thiosemicarbazide. These precipitates are free from the unwanted by-products which often render interpretation of periodate oxidation results somewhat uncertain.

FIG. 3. *Barry's method.*



Enzymic methods of degradation have not yet been developed in the hemicellulose field to the remarkable degree of precision they have reached in starch chemistry, but there is no doubt that they are of rapidly increasing importance and, when methods have been worked out for the separation and purification of the appropriate enzymes, results of major importance can confidently be expected.

As with starch and cellulose physicochemical methods for determining the molecular shape and size are employed to complete the picture of molecular structure. These include *X*-ray analysis, viscosity determinations, and light-scattering and osmotic-pressure measurements. As regards the last-mentioned procedure difficulties often arise in the hemicellulose field in that molecular weights are often in the region 3000—20,000 for which suitable and reliable membranes are not yet available. It is hoped however that as a result of work in progress at the Chemical Research Laboratory, Teddington, membranes covering this important region will be developed but in the meantime it is often necessary to determine molecular weights by the tedious process of isothermal distillation.

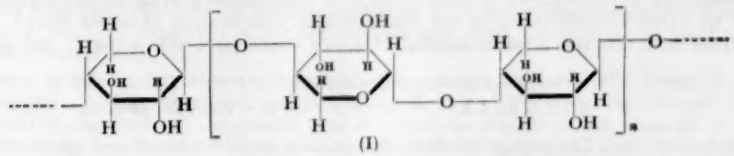
A 1 . . . Residue **. . . 4 X 1 . . .** Residue

(**A** = arabinose; **X** = xylose.)

We may turn now to consider the results achieved when these methods are applied to typical members of the hemicellulose group. The sugar residue most frequently encountered is D-xylose and we can conveniently begin therefore with a consideration of the xylan series of polysaccharides. These are found in all lignified plant tissues and form a very considerable part of the dry weight of all woods, cereal straws, seed coats, and similar materials. The esparto grass used for paper making gives a holocellulose of which some 30% is a xylan readily extractable by alkali. Owing to its accessibility and the widespread importance of the raw material in which it occurs, this xylan has been extensively investigated. As normally obtained it consists mainly of xylose residues but the hydrolysis products usually contain in addition some

[3] Barry, *Nature*, 1943, **152**, 537; Barry, McCormick, and Mitchell, *J.*, 1954, 3692.

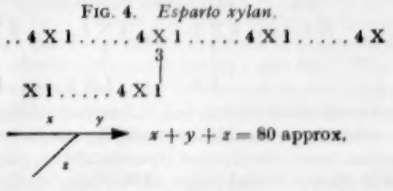
L-arabinose. After methylation and hydrolysis of the fully methylated derivative of the xylan the principal products obtained in the early work in this field were 2 : 3-di-*O*-methyl-D-xylose and 2 : 3 : 5-tri-*O*-methyl-L-arabinose, roughly in the proportions 20 : 1 respectively.[4] The polysaccharide must therefore be built up largely of a series of β-linked . . . 4 X 1 . . . residues (see above), the structure in this respect being very similar to that of cellulose (I). For a long time the rôle of the terminal A 1 . . . residues remained uncertain, and, indeed, this problem has been solved only very recently. The arabinose could be removed easily by mild hydrolysis, leaving a polysaccharide containing xylose residues only and possessing approximately one



(I)

xylose end group for every 20 xylose residues. But the simple interpretation of this in the sense of a chain of . . . 4 X 1 . . . residues terminated at the non-reducing end by A 1 . . ., *i.e.*, the structure A 1—4 X 1 . . . . . 4 X, was not acceptable since further investigation revealed that the proportion of arabinose residues in esparto xylan was not constant, but, on the contrary, varied widely with the methods used to purify the crude xylan. It remained a possibility therefore that the arabinose residues were not combined in the true xylan molecule but were associated with other polysaccharides present as impurities. Steps were then taken to carry out a rigorous fractionation of esparto xylan by methods which would be gentle enough chemically not to disturb the labile arabofuranoside linkages should they be present in the molecule. To do this advantage was taken of the insoluble copper complex which xylan gives in alkaline copper solutions of the Fehling's type. After several such precipitations esparto xylan which originally contained several per cent of arabinose gave fractions which analysed as true xylans containing no detectable amount of arabinose. Investigation of this arabinose-free material by the standard methylation procedure showed that the methylated derivative yielded on hydrolysis 2 : 3-di-*O*-methyl-D-xylose (over 90%) and 2 : 3 : 4-tri-*O*-methyl-D-xylose (2·5%), together with some 2-*O*-methyl-D-xylose and small amounts of other methylated xyloses. After full account had been taken of possible errors due to demethylation during hydrolysis and to other causes it was clear that this particular xylan had a molecular structure composed essentially of chains of 1 : 4′-β-linked xylopyranose residues, with one xylose end group per 40 xylose residues. Molecular-weight determinations indicated, however, that the degree of polymerisation of the methylated xylan was approximately 80, from which it appears that the molecule must contain a single branch. The position of the branch point along the chain is not known, but the isolation of 2-*O*-methylxylose on hydrolysis of the methylated xylan points to a linkage of the 1 : 3′-type at the branch point. Diagrammatically it is possible therefore to represent the main structural features of this fraction of esparto xylan by the formula shown in Fig. 4.[5]

FIG. 4. *Esparto xylan.*



The presence of chains of 1 : 4′-β-linked xylopyranose residues appears to be a general structural feature throughout most of the xylan group of polysaccharides. For maize-cob xylan this has been demonstrated in a particularly elegant way by Whistler and his colleagues at Purdue University.[6] Using the method of partial hydrolysis, they have succeeded in breaking down the xylan extracted from maize cobs into a series of oligosaccharides, ranging from

[4] Haworth, Hampton, and Hirst, *J.*, 1929, 1739; Haworth, Hirst, and Oliver, *J.*, 1934, 1917.
[5] Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289.
[6] Whistler and Tu, *J. Amer. Chem. Soc.*, 1951, **73**, 1389; 1952, **74**, 3609; 1953, **75**, 645.

xylobiose upwards to the heptasaccharide. Separation of these has been effected chromatographically on charcoal–Celite columns, and the individual crystalline sugars have been studied in detail. From the results it is clear that they form a series (Fig. 5), each sugar in which contains one additional xylose residue, the linkages throughout being of the 1 : 4′-β-type. The findings cannot be accounted for on the basis of reversion products and there is clear evidence therefore of the general structural arrangement of the xylose residues in maize-cob xylan.

It is necessary, however, to revert at this stage to the subject of arabinose residues in xylans. At the time when the fractionation of esparto xylan was being studied in this country, A. S. Perlin was investigating in the Ottawa laboratories a very remarkable polysaccharide which he had obtained by careful fractionation of the hemicellulosic constituents of wheat flour.[7] One of the fractions from this was a water-soluble substance which gave xylose (63%) and arabinose

FIG. 5. *Structure of xylose oligosaccharides obtained from maize-cob xylan* (n = 0—6).

X 1[4 X 1]$_n$ 4 X X = β-D-xylopyranose.

(37%) on hydrolysis. The high proportion of arabinose could not be altered by fractionation. The methylated derivative gave on hydrolysis equal amounts of 2 : 3 : 5-tri-*O*-methyl-L-arabofuranose and 2 : 3-di-*O*-methyl-D-xylose, together with 2-*O*-methyl-D-xylose and free D-xylose. The residues of which the polysaccharide is composed must therefore be A 1 . . . ., . . . 4 X 1 . . ., $\begin{matrix}\cdots 4\\ \cdot\cdot 3\end{matrix}$ X 1 . . . and $\begin{matrix}\cdots 3\\ \cdots 4\end{matrix}$ X $\begin{matrix}1\cdots\\ 2\cdots\end{matrix}$ It appears certain from these results that the arabinose residues must be attached to xylose residues in the parent polysaccharide. They could however be removed completely by mild hydrolysis, leaving a true xylan the main structural feature of which was again a chain of 1 : 4′-β-linked xylopyranose residues. Perlin's xylan may therefore be pictured (Fig. 6) as a chain of xylose residues, similar to those in esparto and maize-cob xylans, but with numerous single terminal arabofuranose residues attached as side chains.

FIG. 6. *Wheat-flour xylan.*

X 1 . . . . . 4 X 1 . . . . . 4 X 1 . . . . . 4 X 1 . . . . . 4 X
3 32
1 A 1 A 1 A

Examination of the arabinose-rich, as distinct from the arabinose-free, fractions of esparto xylan revealed a similar state of affairs. Investigations by Aspinall and Moody[8] showed that after methylation and hydrolysis these fractions yielded 2 : 3-di-*O*-methyl-D-xylose (3 parts) and 2 : 3 : 5-tri-*O*-methyl-L-arabinose (1 part), together with 2-*O*-methyl-D-xylose (1 part) and small amounts of tri-*O*-methylxylose and other substances. The relative proportions of these sugars and the absence of lower methylated derivatives of L-arabinose make it certain that the molecule must contain side chains of arabofuranose residues. It follows that much of the xylan present in esparto must conform to the general structure shown in Fig. 7. Whether or not all the molecules are branched is still uncertain, and, as will appear later, there may be further complications in the way of combined uronic acid residues.

FIG. 7. *Arabo-xylan from esparto.*

X 1 . . . . . 4 X 1 . . . . . 4 X 1 . . . . . 4 X
3 3
1 A 1 X 4 . . . . . 1 X

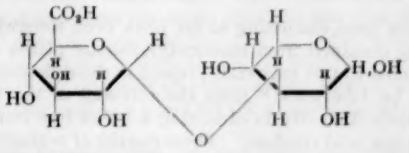
Still greater complexity of structure has been observed amongst the xylans present in cereal straws. Wheat-straw xylan, in particular, has been the subject for detailed study and evidence concerning its structure has been contributed by several groups of workers, including Roudier,[9] Adams[10] and Bishop,[10] F. Smith,[11] and Aspinall.[12] Once again it is found that fractions of different arabinose contents can be separated and, although in this instance it has not yet been possible to isolate material completely free from arabinose residues, some fractions containing only insignificant proportions of arabinose have been isolated.[11] In addition to arabinose

[7] Perlin, *Cereal Chem.*, 1951, **28**, 370, 382.
[8] Aspinall, Hirst, Moody, and Percival, *J.*, 1953, 1631.
[9] Roudier, *Compt. rend.*, 1953, **237**, 840; *Assoc. tech. ind. papetiere Bull.*, 1954, 53.
[10] Adams, *Canad. J. Chem.*, 1952, **30**, 698; Bishop, *ibid.*, 1953, **31**, 134.
[11] Ehrenthal, Montgomery, and Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 5509.
[12] Aspinall and Mahomed, *J.*, 1954, 1731.

this xylan gives rise on hydrolysis to D-glucuronic acid (*ca.* 4%) and possibly to some 4-*O*-methyl-D-glucuronic acid also. There is decisive evidence that the uronic acid residues are combined directly with D-xylose in the xylan macromolecule. In general the glycosidic link of a uronosyl compound is strongly resistant to hydrolysis and on partial hydrolysis of wheat-straw xylan an aldobiuronic acid can be obtained, consisting of a glucuronic acid linked through its reducing group to a xylose residue. On methylation, followed by hydrolysis of the product, a partially methylated xylose containing methyl groups in the 2- and the 4-position is obtained.[10] In other experiments a partially methylated aldobiuronic acid was isolated on hydrolysis of the methylated xylan and this gave on further hydrolysis 2 : 3 : 4-tri-*O*-methylglucuronic acid and 2-*O*-methylxylose.[12] The linkage in the aldobiuronic acid must therefore be of the 1 : 3′-type and its structure must be (II).

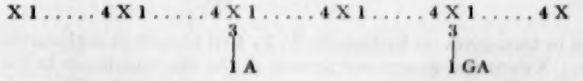
The main structural feature of the polysaccharide is again a chain of 1 : 4′-linked β-xylopyranose residues. Xylopyranose end groups (linkage X 1 . . .) are found to the extent of 2·5%. On the basis of this evidence the general type of structure present in the molecule of wheat-straw xylan is given in Fig. 8 which depicts a chain of xylose residues to which are attached at intervals short branches consisting respectively of single residues of D-glucuronic acid and

(II)



L-arabinose, the branch points being at $C_{(3)}$ of the xylose residue concerned. Very recently a direct proof has been given of the attachment of L-arabinose residues to the main chain of xylose residues. This has been achieved by enzymic breakdown of wheat-straw xylan by a pentosanase enzyme obtained from *Myrothecium verrucaria* which has been found by Bishop and Whittaker[13] to bring about the hydrolysis of . . . X 1–4 X 1 . . . links without a comparable effect on the A 1–3 X . . . links. In this way a series of oligosaccharides has been isolated from wheat-straw xylan, each of which has been shown to contain at least one arabinose residue directly linked to a xylose residue.

FIG. 8. *Wheat-straw xylan.*



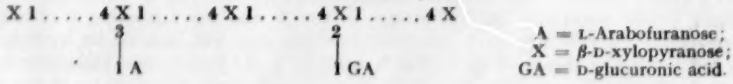
As in the case of the esparto xylans no more than a start has been made in the assignment of structural details in the wheat-straw group of xylans. Nevertheless it seems clear that here again we have to deal with a large group of polysaccharides with very similar main-chain structures but with very varied proportions of side chains. We do not yet know where in the main chain these side chains are attached and whether they occur in a regular pattern or are randomly located along the main chain. No clear evidence is yet available as to whether the main chain is linear or branched, and although there is concrete evidence in favour of $C_{(3)}$ branch points the possibility that $C_{(2)}$ branch points also occur cannot yet be ruled out. The degree of polymerisation of the various molecular species has yet to be determined in detail but preliminary evidence obtained by Greenwood for material examined in Edinburgh indicates a rather small molecular weight of the order of 50 xylose residues. It may well be, however, that the hemicelluloses as they exist in the plant have higher molecular weights. Evidence pointing in this direction is provided by Bishop[14] in his study of crystalline xylans obtained by autoclave treatment of hemicelluloses from wheat and other types of straw. A puzzling feature, recorded by Roudier, is that on removal of the arabofuranose residues by gentle hydrolysis, wheat-straw xylan gives a product containing one xylose end group per 18 residues. An exactly similar observation was made in the early days of the study of esparto xylan and the question naturally arises whether we have here something of special significance in xylan chemistry.

The study of xylans derived from other cereal strains has not yet reached the same stage of detail, but enough is known of the general properties of the xylans of barley straw and oat

[13] Bishop and Whittaker, *Chem. and Ind.*, 1955, 119.
[14] Bishop, *Canad. J. Chem.*, 1953, **31**, 793; cf. Yundt, *TAPPI*, 1951, **34**, 89.

straw,[15] to permit the conclusion that they are in general similar in constitution to wheat-straw xylan. In the case of the material from barley straw fractionation *via* the copper complex can be carried to a point where the arabinose content is probably not structurally significant. Such fractions still contain small but significant quantities of uronic acid residues. Fractions

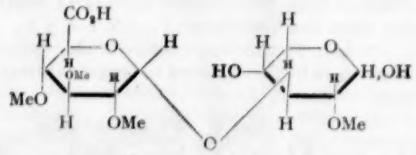
FIG. 9. *Oat-straw xylan.*



of oat-straw xylan containing both arabinose and uronic acid residues have been examined and it appears that the general structure suggested for wheat-straw xylan may apply in these cases also (Fig. 9). There is some evidence that branch points of both the 1 : 3′-type and the 1 : 2′-type may be present in the same molecule. The glucuronic acid (which may be partly present as 4-*O*-methyl-D-glucuronic acid) is combined with xylose by a 1 : 2′-link of the kind found in beechwood xylan (see below). It is possible, but not certain, that the main xylose chain is branched.

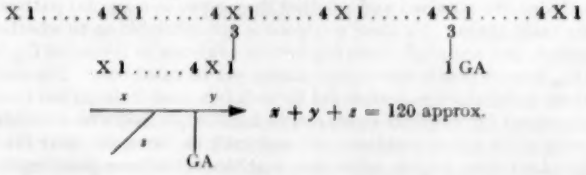
The xylans we have been discussing so far have been somewhat similar in respect of their botanical origin, being obtained from monocotyledonous plants of the grass type. For comparison we may turn now to two materials present in dicotyledonous plants. The first of these is the xylan isolated by Isherwood[16] from the cell-wall of the fruit of the pear (Constance). In this case there is little difficulty in obtaining a xylan free from arabinose, but containing a small proportion of uronic acid residues. These consist of D-glucuronic acid, possibly with some 4-*O*-methyl-D-glucuronic acid but this is not certain. The fully methylated derivative of the pear cell-wall xylan gives on hydrolysis 2 : 3-di-*O*-methyl-D-xylose, 2 : 3 : 4-tri-*O*-methyl-D-xylose, some 2-*O*-methyl-D-xylose, and a partially methylated aldobiuronic acid (III). The

(III)



last substance in turn gives on hydrolysis 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid and a monomethylxylose. Xylose end groups are present in the macromolecule to the extent of 1 part in 60 whilst the percentage of uronic acid is rather less than one. The molecular weight of the methylated derivative corresponds to some 120 residues and on the basis of this evidence the structure of pear cell-wall xylan would appear to be of the type shown in Fig. 10.[17] The posi-

FIG. 10. *Pear cell-wall xylan.*



tions of the branch points at which the side chains are attached are not yet known, and it is to be remembered also that the identification of $C_{(3)}$ of a xylose residue as the point of attachment of the uronic acid side chains rests mainly on chromatographic differentiation between 2-*O*-methylxylose and the corresponding 3-derivative. In consequence it is not yet altogether ruled out that the linkage in the aldobiuronic acid may be GA 1 —2 X.

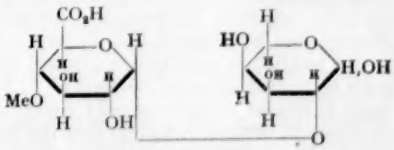
[15] Aspinall, unpublished results; Aspinall and Wilkie, unpublished results.
[16] Isherwood and Jermyn, unpublished results; see also Jermyn "Cellulose and Hemicelluloses" in "Modern Methods of Plant Analysis," Vol. II, Springer-Verlag.
[17] Chanda, Hirst, and Percival, *J.*, 1951, 1240.

From beechwood, by extraction with dilute alkali without previous delignification, Macdonald,[18] of the Forest Products Research Laboratory, isolated a xylan which on hydrolysis gave nearly 90% of D-xylose together with 10% of a uronic acid and a trace of L-rhamnose, which, however, is almost certainly present as an impurity. Structural investigations in Edinburgh by Aspinall and Mahomed[19] have shown that this is a most interesting substance possessing some quite unexpected structural features. The uronic acid turned out to be 4-*O*-methyl-D-glucuronic acid, which although of rare occurrence in Nature has been found also in mesquite gum, aspen wood, and cotton wood. Investigation by the methylation procedure revealed the presence of the following residues in the macromolecule; X 1 . . . . (1·3%), ... 4 X 1 . . . . (78%), $\begin{matrix}\cdot\cdot\cdot\cdot 4\\ \cdot\cdot\cdot\cdot 2\end{matrix}$ X 1 . . . . (9·5%). In addition aldobiuronic acid residues were present to the extent of 10·5%.

The tetra-*O*-methylaldobiuronic acid obtained by partial hydrolysis of fully methylated beechwood xylan gave after reduction by lithium aluminium hydride, followed by further hydrolysis, 2 : 3 : 4-tri-*O*-methyl-D-glucose and 3-*O*-methyl-D-xylose. The fully methylated aldobiuronic acid, again after reduction and hydrolysis of the product, gave rise to 2 : 3 : 4-tri-*O*-methyl-D-glucose and 3 : 4-di-*O*-methyl-D-xylose. The original xylan gave all its uronic acid as 4-*O*-methyl-D-glucuronic acid and there can be no doubt in this case that in the aldobiuronic acid the linkage is 1 : 2′ and that the aldobiuronic acid is 2-(4-*O*-methyl-α-D-glucuronsyl)-D-xylose (IV). We can therefore depict the main structural features of this xylan as a chain of β-1 : 4′-linked D-xylose residues, having one terminal xylose residue for every 80, with side chains of 4-*O*-methyl-D-glucuronic acid, attached on the average to every tenth xylose residue by a 1 : 2′-link (Fig. 11).

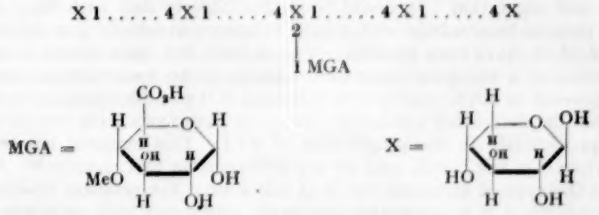
The presence in corn-cob hemicelluloses of 4-*O*-methyl-D-glucuronic acid residues in 1 : 2′-type linkage has been reported by Whistler, Conrad, and Hough[20] who isolated the

(IV)



aldobiuronic acid, 2-*O*-(4-*O*-methyl-α-D-glucuronopyranosyl)-D-xylose, after partial hydrolysis of the polysaccharide. Whistler and Hough[21] had previously isolated a mixture of 2-*O*-(α-D-glucuronosyl)-D-xylose and 4-*O*-(α-D-glucuronosyl)-D-xylose from the hydrolysis products of corn-cob xylan. Here also it appears that residues both of D-glucuronic acid and of 4-*O*-methyl-D-glucuronic acid occur in the same group of hemicellulosic materials. If the residue GA 1—4 X occurs in any part of the molecule other than the end of a chain it would point to a hitherto unknown type of linkage of main-chain xylose residues through positions other than 1 : 4′.

FIG. 11. *Beech-wood xylan.*



Amidst the variety of structural features described in the preceding sections one feature has remained constant, namely, the nature of the main chains of xylose residues. So versatile, however, is the xylose molecule in forming polymers that still further variations occur in natural

[18] McDonald, *J.*, 1952, 3183.
[19] Aspinall, Hirst, and Mahomed, *J.*, 1954, 1734.
[20] Whistler, Conrad, and Hough, *J. Amer. Chem. Soc.*, 1954, **76**, 1668.
[21] Whistler and Hough, *ibid.*, 1953, **75**, 4918.

products. One of the red seaweeds, *Rhodymenia palmata*, is remarkable in that it accumulates amongst its cell-wall polysaccharides large proportions of a xylan which can easily be leached away from the other components. It is a true xylan, giving only D-xylose on hydrolysis, but when examined by the methylation procedure it reveals a novel structural feature.[22] The methylated derivative gives on hydrolysis 2 : 3 : 4-tri-*O*-methyl-D-xylose (1 part), 2 : 3-di-*O*-methyl-D-xylose (12 parts), 2 : 4-di-*O*-methyl-D-xylose (3 parts), and less than 1 part of monomethylxyloses. All attempts to separate either the original or the methylated xylan into separate components have failed and the conclusion seems inescapable that in this substance we have a linear main chain containing both 1 : 4′- and 1 : 3′-linked xylose residues (Fig. 12),

FIG. 12. *Algal xylan from* Rhodymenia palmata.

X 1 . . . . . 4 X 1 . . . . . 3 X 1 X

Number of residues per molecule: X 1, 1; 4 X 1, 12; 3 X 1, 3.

X = β-D-Xylopyranose residue.

these being present in the proportions of 4 : 1, respectively. The chain containing these two types of residue is terminated by a xylopyranose unit and in the particular sample of methylated algal xylan we examined the chain was a short one containing only some 17 xylose residues. Nothing is yet known concerning the order in which the 1 : 4′- and 1 : 3′-links are arranged in the linear molecule.

The position here is somewhat reminiscent of that established for lichenin in which 1 : 4′- and 1 : 3′-linked β-D-glucose residues are present in the same main chain. Recently it has been established that precisely the same kind of structure, containing both 1 : 4′- and 1 : 3′-links, occurs in *iso*lichenin where the glucose residues are combined as α-glucosides.[23] It is interesting to find similar structural features in the hemicellulose designated barley gum, which has recently been isolated by Preece[3] and his collaborators from barley grains. It has been obtained in a pure condition, free from other polysaccharides, by fractional precipitation by aqueous ammonium sulphate. Structural investigations by Aspinall and Telfer[24] have shown that it gives only D-glucose on hydrolysis. Its rotation is such that β-glucosyl linkages must be present. Its methylated derivative yields on hydrolysis equal amounts of 2 : 3 : 6- and 2 : 4 : 6-tri-*O*-methyl-D-glucose, with a mere trace of tetramethylglucose (end group). The molecular weight determined by Greenwood was about 20,000 and it follows that the molecular structure of the substance must be in the form of a long unbranched chain containing equal numbers of β-1 : 4′- and β-1 : 3′-linked D-glucose residues (Fig. 13).

FIG. 13. *β-Glucosan from barley (barley gum).*

. . . . . 4 G β 1—3 G β 1 . . . . . G = D-Glucopyranose.

It was mentioned at the beginning of the Lecture that, in addition to residues of glucose, xylose, arabinose, and uronic acids, other sugars also, notably galactose and mannose, were encountered in the hemicellulose group. There is indeed a vast and almost unexplored field waiting for investigation, but progress is slow in the meantime owing primarily to difficulties of fractionation and separation. It would be unprofitable to deal with these in detail at the moment, and I propose to conclude with a brief reference to two further substances, detailed investigations of which have been possible. One of them has been chosen from the galactose series and the other is a mannose derivative. Amongst the many components of the hemicellulose group present in larch wood (*Larix europaea*) it is possible to separate with reasonable ease a polysaccharide, designated ε-galactan, which on hydrolysis gives rise to D-galactose and L-arabinose, approximately in the proportions of 6 : 1. This material has been extensively examined by White[25] in the U.S.A. and by my colleagues in this country.[26] There is general agreement as to the type of structure but it is still a very live problem whether the material isolated from larch wood is a single polysaccharide containing both galactose and arabinose residues or whether a portion of it consists of a true galactan, free from combined arabinose. In some early work on the methylated derivative of this galactan evidence was obtained that by careful fractionation it was possible to separate a portion which gave on hydrolysis solely

[23] Chanda and Percival, *Nature*, 1950, **166**, 787.
[25] Chanda and Hirst, unpublished results.
[24] Aspinall and Telfer, *J.*, 1954, 3519.
[25] White, *J. Amer. Chem. Soc.*, 1941, **63**, 2871; 1942, **64**, 302, 1507, 2838.
[26] Campbell, Hirst, and Jones, *J.*, 1948, 774; Aspinall, Hirst, and Ramstad, unpublished results.

D-galactose derivatives. The remainder gave an arabinose derivative (present as end group) and a mixture of methylated galactoses. The evidence at present available points to the presence of the following residues in the galactose skeleton : Gal 1 . . . ., ... 6 Gal 1 . . . . and . . . $^{3}_{6}$ Gal 1 . . . . . The type of structure would, therefore, be that outlined in Fig. 14, and there are indications that in the arabogalactan portion—or in the whole polysaccharide if it is not separable into a galactan and an arabogalactan—arabinose chains are attached at $C_{(6)}$ of some

FIG. 14.

. . . . . Gal β 1—6 Gal β 1 . . . . .
^{3}
|
1 β Gal 6 * Gal = D galactopyranose.

* In the arabogalactan L-arabinose residues may be attached at some of these positions.

of the galactose side chains. It is possible that the situation here is not unlike that in the xylan group where, as we have seen, larger or smaller proportions of L-arabinose residues may be attached to a basal structure composed of xylose residues. There is however a further complication the implications of which are still under active investigation. J. K. N. Jones [27] has recently found that on mild hydrolysis of this L-galactan some of the arabinose residues are removed and that one of the products of partial hydrolysis is a disaccharide 3-(L-arabopyranosyl)-L-arabinose in which arabinose occurs in the pyranose form. He has obtained this same disaccharide after partial hydrolysis of other naturally occurring polysaccharides under experimental conditions which render it unlikely that it is an artefact or reversion product. Only on rare occasions have arabopyranose residues been reported in natural products and this new finding introduces serious complexities into the problems of structural determination in the group which comprises the hemicelluloses, gums, and mucilages.

As an example of polysaccharides of this type containing mannose residues we may consider the mannan (guaran) obtained from the material designated guar. This is unique in that it is the only substance of its class to which it is possible to ascribe a reasonably definite and complete structural formula. It has been investigated in detail by Whistler and his colleagues [28] at Purdue University, who have made use of all the various methods for structural determination including partial hydrolysis, methylation, and *X*-ray investigations. The substance gave D-mannose and D-galatose on total hydrolysis. On partial hydrolysis several products were obtained, including two disaccharides (A) and (B) and two trisaccharides (C) and (D) (Fig. 15). These were separated and their identity proved by rigorous methods. The identification of these products, taken in conjunction with the results of the methylation and other experiments, enabled a unique structure to be assigned to the polysaccharide. In this the D-mannose residues are found as a chain of 1 : 4′-β-linked mannopyranose residues to which is attached at $C_{(6)}$ of

FIG. 15.

(A) Mβ 1—4 M Mβ 1—4 Mβ 1—6 M (C)
(B) Galα 1—6 M Galα 1—6 Mβ 1—4 M (D)

Gal = D-galactopyranose; M = D-mannopyranose.

every alternate mannose residue an α-linked D-galactopyranose residue as a side chain (see Fig. 16). It is of interest to recall in this connection that 1 : 4′-links are of common occurrence in mannose-containing polysaccharides, prominent features being, for instance, in the structure of the mannans of the ivory nut.

FIG. 16. *Guaran.*

Galα 1
|
6
. . . . . 4 Mβ 1—4 Mβ 1 . . . . .

These examples will, I hope, give some idea of the kind of problems encountered in the field of hemicellulose chemistry. It will be all too evident that there exist many gaps in our knowledge of this important group of natural products, and in indicating these deficiencies I can

[27] Jones, *J.*, 1953, 1672.
[28] Ahmed and Whistler, *J. Amer. Chem. Soc.*, 1950, **72**, 2524; Whistler and Durso, *ibid.*, 1951, **73**, 4189; 1952, **74**, 5140; Whistler and Smith, *ibid.*, 1952, **74**, 3795.

perhaps claim to have fulfilled some of the obligations imposed upon the Pedler Lecturer. He is required, however, to undertake a still more onerous task, namely, to indicate the general direction of future developments in the field of his Lecture. No prophecies concerning the outcome of scientific research are safe and this applies with particular force to structural investigations, where a discovery in another and apparently unrelated field may be seized upon to open up entirely new possibilities of exploration. Amongst the clamant needs at the moment are better methods of separating closely related polysaccharides. In the hemicellulose field this may be assisted in the not too distant future by the use of improved ionophoretic methods. It seems certain also that as our knowledge of pentosanase enzymes is increased much more use will be made of enzymic methods of degradation for structural determinations. Degradation by partial hydrolysis, whether by acids or enzymes, coupled with improvements in the chromatographic separation of oligosaccharides will go far to solve troublesome problems concerning the order in which the sugar residues occur in the macromolecule. But the determination of a structural formula is by no means the final goal of the worker interested in these problems. That is only one step towards the still more difficult problem of the phytochemical origin of the various sugar residues found combined in the hemicelluloses. A few years ago it was attractive to speculate on the possibility that the two pentoses encountered so frequently in this group, namely, D-xylose and L-arabinose, could be derived simply from D-glucose and D-galactose respectively, by simple oxidation at $C_{(6)}$ followed by decarboxylation. It is abundantly clear however from the structural determinations which have already been made, that the transformation of a hexosan into a pentosan is not effected at the polysaccharide level by simple changes of this kind. At the very least hydrolysis to monosaccharide units must be effected before transformation to a new sugar residue and rebuilding takes place, and some recent work by Hough and Jones [39] on the action of aldolase enzyme systems has indeed given hints that before the synthesis of pentose-containing polysaccharides can take place, further degradation of hexose units to triose and biose systems may be necessary. I venture to think that in the near future much attention will be paid to these problems concerning the synthesis of polysaccharides by cytoplasmic enzyme systems, and that in this difficult field all the resources of chemistry and biochemistry, including the extended use of radioactive tracer elements, will necessarily be called into play. The present gaps in knowledge are indeed large and formidable, but in assessing them it is perhaps not unfitting to recall that structural polysaccharide chemistry is a discipline of comparatively recent origin, dating back indeed less than 30 years. Much has been accomplished in that short time and with the aid of methods already available and in view we can confidently expect still more rapid progress in the future.

[39] Hough and Jones, *J.*, 1952, 4047, 4052; 1953, 342; Gorin and Jones, *J.*, 1953, 1537; Gorin, Hough, and Jones, *J.*, 1953, 2140.

OBITUARY NOTICES.

SIR SHANTI SWARUP BHATNAGAR.

1894—1954.

The sudden death of Sir Shanti Bhatnagar removed from the field of Indian science a dynamic personality. The great services he rendered to science in India will be remembered for generations to come. He was born on February 21st, 1894, at Bhera, District Shapur, now in West Pakistan, and when he was only eight months old he lost his father. He had to struggle his way up as a student. After taking the M.Sc. degree of the Punjab University from the Forman Christian College, Lahore, he went to England in 1919 and worked till 1921 in the Physical Chemistry Laboratory of University College, London, under Professor F. G. Donnan. There he met two other young chemists from India, J. C. Ghosh and J. N. Mukherjee. Professor Donnan was very sympathetic and affectionate in his relations with them : in fact, this was characteristic of Professor Donnan in his dealings with all the young men who came to work under him. Bhatnagar, Ghosh, and Mukherjee later came to be known in some scientific circles of England as the " three musketeers " of Donnan. Under Professor Donnan's directions Bhatnagar took up the study of phase inversion in emulsions. The degree of Doctor of Science of London University was awarded to him on the basis of the contributions he made to our knowledge of this subject.

On return to India, Bhatnagar joined the newly established Benares Hindu University as Professor of Chemistry. He was successful in attracting a number of young men for collaboration in his research and soon developed an active centre of research in colloids and other branches of physical chemistry. His zeal and ability as an organizer also made their effect felt in the affairs of the University. In 1920 he joined the Punjab University as a Professor of Physical Chemistry and Director of the University Chemistry Laboratories at Lahore; he held these positions till 1940. His laboratory soon became a prominent centre of scientific research in India. Important contributions were made by Bhatnagar and his co-workers in the fields of colloids, surface chemistry, and magnetochemistry. With Mr. R. N. Mathur, he devised in 1935 a magneto-interference balance which was manufactured by Adam Hilger & Co. In collaboration with Mr. K. N. Mathur he brought out a book entitled " Principles and Application of Magneto Chemistry," published by Macmillan Ltd., probably the first book on the subject in English. While at Lahore he also undertook investigations on some problems of oil technology with the financial support of Messrs. Steel Brothers & Co. Ltd. and made important contributions in this field. He was instrumental in securing donations for chemical research in the laboratories under his charge, and himself contributed to them from the fees he received from commercial firms.

Soon after the outbreak of World War II, the Government of India decided to establish a Directorate of Scientific and Industrial Research and in 1940 a start was made with Bhatnagar as Director. The history of its development, especially in its earlier days, reveals the unique qualities Bhatnagar had of enlisting the active support and co-operation of all persons whose influence counted in the furtherance of projects he had in view. He had the gift of winning over opposition and getting on well with men of diverse types and interests. Socially he was most approachable, warm-hearted, and hospitable. He lived an unostentatious life. He could, however, be pugnacious if the situation required, but mostly kept his own counsel.

Bhatnagar belonged to a generation which witnessed the rapid development of scientific research and scientific institutions in India. The establishment of the University College of Science and Technology in Calcutta and the appointment of (later Sir) P. C. Ray and (later Sir) C. V. Raman as Palit Professors of Chemistry and Physics respectively were instances of the outward expressions of the strong need felt by Indian leaders for the promotion of science and scientific research. In this development quite a number of Indian scientists, including Bhatnagar, played a very active rôle. Honours came to him in due course and he held the offices of the President of the Indian Chemical Society, the President of the Section of Chemistry of the Indian Science Congress Association, and later General President of the Indian Science Congress Association and President of the National Institute of Sciences in India. He was awarded the O.B.E. in 1936 and was knighted in 1941. In 1943 he was elected a Fellow of the Royal Society and also an honorary member of the Society of Chemical Industry. He led a

number of scientific delegations to International Scientific Conferences and was awarded the honorary degree of D.C.L. by the University of Oxford on one of these occasions. Perhaps his greatest claim to be remembered lies in his success in developing the Directorate of Scientific & Industrial Research, culminating in the establishment of twelve National Laboratories and of the Ministry of Natural Resources & Scientific Research of the Government of India. In all these endeavours he was fortunate in having the most active encouragement, help, and fostering care of Mr. Jawaharlal Nehru, Prime Minister of India. In 1954 he was made a Padma Bibhusan, Dusra Varg (Second Order).

He was an indefatigable worker with almost unlimited energy. Insomnia, which he suffered from, never restrained his energy. He was greatly helped by his wife who was a charming host and most unassuming. She quietly looked after all his needs. Her death in 1946 was a great loss to him and he gave vent to his feelings in Urdu verses, an activity of which he was greatly fond but which he could rarely indulge because of pressure of other work. He claimed to be a member of the " Bramho Samaj " known also as " Prarthana Samaj," a reformist group of the Hindu Society who did not believe in caste distinctions and idol worship. All who came to know him will remember him, not only for his striking achievements, but also for his intensely human qualities.

J. N. Mukherjee.

JOHN STANLEY HERBERT DAVIES.

1893—1954.

John Stanley Herbert Davies was born in Kingsland, near Hereford, on June 27th, 1893, and was educated at Abertillery County School and Llandovery College. Proceeding to Emmanuel College, Cambridge, he obtained his B.A. in the Natural Science Tripos in 1916, having studied chemistry, physics, and zoology. During the war Davies was with the Royal Engineers but returned to post-graduate research at Manchester College of Technology and obtained the M.Sc. (Tech.) and later the Ph.D. degree (1924). With the aid of a D.S.I.R. maintenance award, the period of training under Professor F. M. Rowe led to several very interesting publications (*J.*, 1920, **117**, 1344; 1922, **121**, 1000) and in particular to a paper (*J. Soc. Dyers and Col.*, 1926, **42**, 242) which was awarded the Gold Medal for the year by the Dyers' Company. This work described the preparation of phthalazine, phthalazone, and phthalimidine derivatives by a new reaction of diazosulphonates from 2-naphthol-1-sulphonic acid.

Davies was engaged on research work with " mustard gas " at the War Office Establishment, Sutton Oak, St. Helens, from 1925 to 1930 and the results have been published in two papers (with Phillips and Mumford, *J.*, 1929, 535; with Oxford, *J.*, 1931, 224). The greater part of his career was spent as a research chemist in the Dyestuffs Division of Imperial Chemical Industries Limited, Blackley. He was concerned with problems connected with the development of phthalocyanines and the eventual launching of Monastral Blue. On transferring to the Medicinals Section he worked at first on synthetic œstrogens of the tri-*p*-methoxyphenylethylene type, on quaternary ammonium bactericides, and on *X*-ray contrast agents. In September, 1941, he was seconded to Oxford to work with Sir Robert Robinson on synthetic problems related to the steroids, but returned to Blackley in December 1943 to join the research team on penicillin. Davies was associated with several reports to the " Committee on Penicillin Synthesis " and details are given in " The Chemistry of Penicillin," Princeton University Press, 1949.

His appointment as Director of Research to British Schering Research Laboratories Limited, at Alderley Edge, allowed considerable scope for work on compounds of chemotherapeutic interest. In particular two fields were specially covered and led to an examination of oxazolidones and furanochromones. The alkylation of oxazolid-2 : 4-diones and 2-thio-analogues was accomplished in collaboration with Hook and led to improved methods for the preparation of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, of importance in the treatment of " petit mal " (*J.*, 1950, 30, 34, 36). In the furanochromone field there were many developments, including the synthesis of visnagin and related compounds (with Norris *et al.*, *J.*, 1950, 3195, 3202, 3206), after kellin had been synthesised in the same laboratories (*J.*, 1949, 530). There was also collaboration with Professor J. M. Robson of Guy's Hospital Medical School in the examination

of some analogues of triphenylethylene in relation to sex-hormone activity (*Brit. J. Pharmacol.*, 1950, **5**, 376).

From December 1950 Davies was a lecturer at the Royal Technical College, Salford, in the Department of Chemistry and Applied Chemistry. Here he was associated with the teaching of organic chemistry and began the first research work at the College in synthetic organic chemistry. This was concerned with a continuation of furanochromone chemistry and culminated in the award of the first Ph.D. to a student of the College by London University. Davies also had his influence on the laboratory work and made an excellent selection of special preparations for advanced work. He was elected to the Fellowship of the Royal Institute of Chemistry in 1952.

In his own experimental work Davies showed great patience and was keen and methodical. He certainly excelled in the production of first-class specimens of his various products although the procedure was most time-consuming. His useful books of collected references, on lines of special interest, were often consulted.

After going to Wilmslow in 1945 Davies had very little by way of outside activities, but maintained his garden in its lovely condition. He died suddenly at his home on July 26th, 1954, and is survived by his widow, with whom great sympathy is felt by all who knew them.

G. R. Ramage.

HENRY STANLEY RAPER.

1882—1951.

When Henry Stanley Raper died unexpectedly on December 12th, 1951, chemical physiology lost an outstanding worker with unusual qualities of scientific insight allied to patient thoroughness—not to speak of a degree of genuine modesty which is possessed only by the truly great—and the cause of medical education a devoted and well-loved servant. I use the term " chemical physiology " advisedly, for it means something a little different from the fashionable word " biochemistry " and it is the term that he himself always used.

Born on March 5th, 1882, at Bradford in Yorkshire, the last but one of a large family, he first studied chemistry with the object of qualifying himself as a dye-works chemist, but becoming aware that he suffered from partial colour blindness his interests as a student of chemistry naturally turned away from dyes. After some time spent at Bradford Technical College, he entered Yorkshire College, Leeds, then a constituent college of the old Victoria University, and obtained the degree of B.Sc. in 1903. Later he carried out organic chemical research under Julius B. Cohen with whom his first three papers were published in this *Journal*. In Cohen's department he met H. D. Dakin—afterwards to become a famous investigator of intermediary metabolism—and it was probably the influence of these two men which aroused Raper's interest in what was to be his life's work, the application of chemistry to physiological studies. The award of an 1851 Exhibition enabled him to go to the Lister Institute in 1904 where with J. B. Leathes he began work on one of the two main topics of his working life, the metabolism of fats. A year spent in Hofmeister's laboratory in Strasbourg introduced him to the complexities of the chemistry of proteins and their breakdown products, thus awakening an interest which was still apparent twenty-three years later when he asked the present writer to undertake, as a Ph.D. topic under his direction, a study of plastein formation, then believed to be an example of enzymic protein synthesis. After another year with Leathes he studied for a medical qualification which he obtained at Leeds University in 1910, and then joined Leathes in Toronto, where the latter had gone to found a Department of Pathological Chemistry. After three years there as Lecturer in Pathological Chemistry, during which time he also taught chemistry in the Ontario Dental School, he returned to Leeds to a post in the Physiology Department, where he was subsequently appointed Professor. This period was broken by service, during the first World War, in the Anti-Gas Department of which he eventually became head and for which work he was awarded the C.B.E. in 1918.

In 1923 came his last move, when he was invited to succeed A. V. Hill as Brackenbury Professor of Physiology in the University of Manchester. He occupied this Chair with great distinction until he retired from it and from the administrative burden associated with the Directorship of the Physiology Laboratories in 1946, to become Dean of the Manchester University Medical School with the title of Professor of Chemical Physiology. In this capacity he was

able to continue to render the great services to medical education and to the University of Manchester which had occupied him along with his scientific researches during his years as holder of the Brackenbury Chair. He died a few months before he was due to retire from the University he had served so well for twenty-eight years, just when he could look forward to more leisure to enjoy those pursuits which he loved—the cultivation of his lovely garden at Prestbury in Cheshire and the water-colour drawing at which he was no mean executant despite his defect in colour vision.

His two main fields of interest as a chemical physiologist were fat metabolism and the mode of formation of melanin. Upon the former of these subjects he first worked with Leathes and later published papers with H. D. Kay, P. W. Clutterbuck, and others. With B. Cavanagh he was the first in this country to use deuterium as an indicator in studies of fatty acid metabolism, being anticipated in this by Schoenheimer and Rittenberg in the United States by only a few months. His interest in fat metabolism was maintained for the rest of his life, as is evident from the fact, that, shortly before he died, he gladly accepted, to the general delight, an invitation from the Biochemical Society to preside at their 1952 Symposium on Lipid Metabolism. He took much trouble over the preparation of his opening address and though his death deprived the meeting of the privilege of hearing him deliver it in person its preparation was sufficiently advanced for it to be appropriately read to the meeting from the Chair.

The main work for which H. S. Raper was known, and upon which his reputation in the history of chemical physiology will securely rest, is his outstanding feat in elucidating the sequence of reactions by which tyrosine under the influence of the enzyme tyrosinase is transformed into the black pigment, melanin. In this work, in which A. Wormall, F. C. Happold, and others participated over the years, a complicated series of changes was unravelled step by step and it will always rank as a classic piece of work on the mode of action of an enzyme carried out before the introduction of isotopic tracers made such achievements relatively easy. It was in this work especially that his early training as a chemist stood him in good stead; he had the ideal equipment for a chemical physiologist, a flair for chemistry founded on a sound chemical training combined with an essentially physiological outlook.

By any reckoning H. S. Raper must be counted among the great physiological chemists which Britain has so far produced and a fair share of worth-while honours came his way. He was elected to the Royal Society in 1929 and served as a member of its Council from 1939—41 and as a Vice-President from 1940—41. In 1947 his old University, Leeds, conferred upon him the degree of LL.D. *honoris causa*. His papers were of a consistently high standard, though not numerous in comparison with the output of many men more prone to seek the limelight or more assiduous in taking steps to advance themselves. The reason for this is partly that during his later life he freely sacrificed his own personal interests in favour of devoting himself to furthering the interests of the University and of the Medical School. It mainly, however, resided in his own character and personality. His standards as a man of science were unusually high. One could not for one moment connect Raper with anything smacking the least bit of the meretricious. He was the last man to rush into print until he was sure of his ground and had done a thorough and honest craftsman's job. Moreover, his principles would not let him build a reputation as a prolific genius by making use, as he so easily could have done, of the labours of large numbers of eager young research workers as was the fashion at the time in many continental Institutes. He once told the writer that he regarded this sort of thing as amounting to exploitation—a thing of which he did not in the least approve. Nevertheless, he trained and inspired by his example a good number of men who later came to occupy, with distinction, Chairs of biochemistry or physiology or other posts of similar standing, all of whom would gladly testify to his outstanding qualities as a kindly, modest man of unusual integrity, a truly great man under whom it was a unique privilege to work. Indeed, his former pupils and associates had planned to do honour to him on the occasion of his retirement by entertaining him to dinner on the evening of the aforementioned Biochemical Society Symposium and presenting him with a specially bound volume made up of one reprint each from all those of his former collaborators who could be reached. Unhappily his death robbed them of the opportunity of showing their affection for, and gratitude to, him in a way which would surely have given him great pleasure; but it is certain that none of them will forget the happy and fruitful years spent in the laboratory of "The Great White Chief."

S. J. Folley.

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